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CONTENTS

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THE CLINICAL MANIFESTATIONS OF NICOTINIC ACID AND RIBOFLAVIN DEFICIENCY (PELLAGRA) *

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THE genesis of spontaneous deficiency disease in human beings is such that it is quite unlikely that an uncomplicated avitaminosis should occur. This is particularly the case in deficiencies of the B group of vitamins. These substances commonly occur together in their natural sources and have closely related functions in essential metabolic processes so that any circumstance which causes inadequate intake, poor utilization or rapid depletion of one of these vitamins is almost certain to affect the whole group. The title of my lecture suggests that pellagra is a combination of nicotinic acid deficiency and ariboflavinosis. This is only partly true, evidences of thiamin deficiency are seldom absent and, as knowledge increases, it is likely that evidences of other avitaminoses may be recognized.

The term pellagra implies the presence of symmetrical, definitely localized dermatitis which in our present state of knowledge is considered a specific manifestation of nicotinic acid deficiency. It is conservative to think of pellagra as a B group avitaminosis in which lack of nicotinic acid is predominant but in which other vitamins are depleted to a level of physiologic inadequacy. Since many persons with B group deficiencies fail to develop dermatitis it seems necessary to abandon the term "pellagrous" for those manifestations of the syndrome not characterized by typical skin lesions and to refer to them in terms of the specific avitaminosis shown to be concerned.

Recognition of the symptoms and signs of predominant avitaminoses has become possible only since adequate supplies of pure synthetic vitamins have been available for differential clinical tests. Coincidentally it has been possible to correlate the probable chemical activities of the vitamins with their physiologic functions in health and to link the manifestations of deficiency diseases with perversion of these functions. When Elvehjem and his asso-

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ciates [1] demonstrated the importance of nicotinic acid in nutrition and Sebrell and Butler [2, 3] discovered the signs of riboflavin deficiency in human subjects, it was immediately suspected that the clinical significance of these observations depended on the participation of nicotinic acid and riboflavin in various metabolic processes already well known to physiologists and biochemists.

The derivation of energy from carbohydrate foods and certain respiratory processes of cells depend on the chemical activity of compounds of the B group of vitamins with phosphoric and adenylic acids. The utilization of carbohydrate is a matter of fractional dehydrogenation, which is the chemical equivalent of oxidation, followed by decarboxylation. Nicotinic acid is the chemically active fraction of the coenzymes diphosphopyridine nucleotide (coenzyme I) and triphosphopyridine nucleotide (coenzyme II) which are essential to the intermediate metabolism of glucose. Thiamin is the reactive portion of cocarboxylase (diphosphothiamin). Riboflavin is, similarly, the active residue of the " coferment " of Warburg, which is ubiquitous in cells and concerned with many enzyme reactions; also it is thought to function as an intracellular respiratory ferment in the absence of haem.

Triphosphopyridine nucleotide is active in the oxidation of hexose monophosphate. The aldehyde group of the sugar is oxidized, with reduction of the pyridine nucleotide. A specific protein from red blood cells (or yeast) which unites both with hexose monophosphate and triphosphopyridine nucleotide must be present. The reduced nucleotide is oxidized by flavoprotein and so regenerated, flavoprotein in turn is oxidized by molecular oxygen. Diphosphopyridine nucleotide functions in the utilization of hexose diphosphate. After the cleavage of hexose diphosphate into two molecules of triose phosphate, diphosphopyridine nucleotide dehydrogenates (oxidizes) triose, losing oxygen which is restored by flavoprotein, the reduced flavoprotein is in turn reoxidized by molecular oxygen, possibly from haem. The phosphoglyceric acid resulting from the dehydrogenation of triose undergoes a series of enzymatic reactions with the production of phosphopyruvic acid. This, in the presence of adenylic acid is decomposed into pyruvic acid. Pyruvic acid may be broken down by two systems. By the combined action of diphosphothiamin (cocarboxylase) and the flavoprotein-cytochrome chain, it is oxidized to CO_2 and H_2O. In the absence of molecular oxygen, pyruvic acid yields oxygen to reduced diphosphopyridine nucleotide, being converted into lactic acid, while the pyridine nucleotide is regenerated.

Thiamin, nicotinic acid and riboflavin are thus concerned with the continuous processes of cellular nutrition and respiration and while they function in part as activators which are continually regenerated, they also are components of coenzymes which are used up and require constant replacement. All three vitamins are probably normally present in all cells. The symptoms and signs of avitaminosis may be regarded as results of chemical disturbances of cellular function due to failure of coenzyme action. The clinical phe-

nomena depend on the grade of vitamin depletion and the rapidity with which it is brought about.

The factors which contribute to the production of clinical manifestations of vitamin deficiency are many and often their influence seems obscure or even paradoxical. The fundamental mechanism is the effort of the body to derive energy from carbohydrates in excess of the available supply of vitamins. The physiologic processes are normal in so far as intrinsic cellular metabolism is concerned; disease results from failure of the extrinsic supply of substances necessary to replenish the coenzymes. Inadequate diet is the common cause of endemic avitaminoses though many other factors are active. The nature of an inadequate diet is still widely misunderstood and starvation is constantly confused with bad nutrition. An inadequate diet may be, in fact usually is, of high caloric value because of its high carbohydrate and fat content. Bleached wheat flour, highly milled cornmeal, glucose syrup, lard and fat pork are the main constituents of such a diet. The use of soda or baking powder instead of yeast to leaven bread made of flour or cornmeal and the substitution of hominy grits for potatoes are contributing factors. The dietary vagaries of individuals who for various reasons abstain from the common protective foods are a common and frequently overlooked source of nutritional disease. The use of an inadequate diet seldom or never produces complete or acute avitaminosis since no naturally selected diet is apt to be completely lacking in any single vitamin. In the course of time, however, chronic partial deficiency produces functional and organic changes which interfere with the absorption or utilization of the small amounts of vitamins available so that finally, a critical level of depletion is reached.

In individuals whose nutritional balance is chronically poor but still adequate at a given level of metabolism, any factor which creates an increased demand for the utilization of energy may precipitate the clinical manifestations of avitaminosis by causing the rapid depletion of coenzymes. The common conditions encountered clinically are unaccustomed work, fever, pregnancy, and hyperthyroidism, the substitution of alcohol for food and therapeutic maintenance on parenterally administered glucose. The derivation of energy from alcohol involves the same coenzyme functions that are active in the metabolism of glucose and when the daily intake of alcohol is sufficient to satisfy a major portion of the caloric requirement, depletion of vitamins is rapid and often clinically complete. It is not generally recognized that "intravenous feeding" with dextrose solutions produces a similar depletion and that many of the severe complications of this frequently necessary procedure are due to avitaminosis. Occasionally when patients with diabetes poorly controlled by relatively low carbohydrate diet and small amounts of insulin are changed to a high carbohydrate regimen with the requisite increase in insulin, acute avitaminosis results, evidently from the greatly increased derivation of energy from glucose.[4]

Loss of ingested vitamins from vomiting or diarrhea is equally as important as severely reduced intake in producing or prolonging avitaminosis. Less obvious causes of deficiency which may attain a serious grade are failure of absorption or utilization of vitamins when adequate amounts are ingested. Gastric achlorhydria seems to be particularly potent in preventing the extraction of vitamins from their natural sources in food. It is well known that achlorhydria is common in all the deficiency diseases. In pellagra it is more frequent than in any of the other syndromes and there is reason to think that atrophy of the gastric mucosa with failure of the acid secreting function is a specific effect of nicotinic acid deficiency. The administration of nicotinic acid frequently results in the reappearance of acid [5] though as long as two years of constant treatment may be necessary to produce this effect.[6] In fatal pellagra the mucosa of the entire gastrointestinal tract is atrophic and while no direct proof can be offered, it seems quite likely that this is a result of prolonged partial deficiency of the B vitamins as well as a contributing factor to the failure of absorption or utilization of the vitamins ingested. It has been shown that the phosphorylation of riboflavin occurs in the mucosa of the small bowel [7] so that atrophy or dysfunction of the mucosa of this part of the intestine may be of equal importance with similar changes in the stomach. Edema of the intestine also interferes with absorption of vitamins and probably contributes to the deficiencies so frequently seen in heart disease, nephritis, cirrhosis of the liver and obstruction of the mesenteric circulation from any cause. It seems probable that edema due to thiamin deficiency may have a similar effect though there are no valid observations. The high incidence of avitaminoses in patients with arteriosclerosis suggests that this condition may contribute to their production. There seem to be at least three possible mechanisms. Diminished capillary circulation resulting from narrowing of arteries and arterioles may interfere with absorption of vitamins from the gastrointestinal tract or it may reduce the amount reaching the peripheral capillary beds of all tissues. The third possibility is loss of these rapidly eliminated vitamins due to the nocturnal diuresis so common in arteriosclerotic disease of the kidneys. In a considerable number of instances of pellagra there seems to be no question of an adequate vitamin intake and no demonstrable failure of absorption; the only logical explanation in such cases would seem to be failure of utilization. Little is known of the factors which condition utilization. It is possible that any disease or serious dysfunction of the liver may interfere with the phosphorylation or storage of thiamin and nicotinic acid or with the storage of riboflavin phosphate. It is also possible that there is definite interrelation of the functions of the B group of vitamins so that marked deficiency of one may prevent the normal activity of the others.

Though much effort has been expended in attempts to find rapid and relatively simple tests for the detection of subclinical grades of deficiency of the B vitamins, no methods are as yet available. It is possible to estimate the concentration of thiamin and nicotinic acid in the blood and of riboflavin

in the urine and it is certain that known methods will be sufficiently simplified to make them useful for diagnosis. For the present the recognition of the pellagrous syndrome depends on familiarity with its various manifestations and the application of therapeutic tests under controlled conditions. It has been possible to identify the symptoms and signs resulting from deficiency of thiamin, nicotinic acid and riboflavin by maintaining patients on a diet extremely poor in all vitamins but supplemented with all but the one under investigation. Once the clinical picture of a relatively pure avitaminosis is determined by this method, the validity of the experiment can be proved by the administration of a single vitamin to patients presenting a specific symptom complex.

Only recently has it been recognized that there is much difference between the clinical manifestations of severe acute and chronic partial deprivation of a vitamin. The evidences of acute avitaminosis are largely functional because the deficiency is produced too rapidly for important tissue changes to occur. In chronic partial deficiencies, functional disturbances occur early, are mild at first but progressively become more severe and finally characteristic anatomical changes are produced. Clinically, all grades of mingling of acute and chronic effects of avitaminosis are seen. Because neurons are more sensitive to disturbances of nutrition and oxygen supply than other cells, signs and symptoms referable to the nervous system are particularly common.

In the chronic partial deficiency of B vitamins which finally results in the syndrome of pellagra, the symptoms and signs of nicotinic acid deprivation are prominent. Mild psychic disorders may precede other manifestations by weeks or months.[6, 8] Neurasthenic complaints of all sorts are common. Slight mental retardation, loss of memory for recent events, apprehension, confabulation, depression or mild delusional states may recur for months or years. Partial deafness, particularly for high pitched tones, may be the presenting symptom.[9] Digestive disturbances, particularly gastric discomfort after meals, burning of the esophagus and stomach, flatulence and constipation are almost invariable, anorexia is very apt to develop, with decreased intake of all sorts of food. Soreness of the tongue, often with no visible glossitis, is a common complaint. In women there is apt to be a concurrent non-specific vaginitis, usually with hyperesthesia and dyspareunia. It is characteristic that such symptoms undergo spontaneous remission and recurrence. Recurrence or relapse is apt to be seasonal, appearing in spring and fall, though it may follow infection, unaccustomed physical exertion or trauma of any sort. As time goes on, food intake is apt to be reduced in the effort to mitigate indigestion or as a result of anorexia. With increasing malnutrition glossitis proceeds to atrophy of the lingual papillae and functional or anatomic changes in the gastric mucosa result in achlorhydria. It is likely that atrophic changes in the intestinal mucosa keep pace with those in the stomach. Diarrhea may be initiated by the presence in the bowel of large amounts of undigested food, by failure of

absorption of fluids by an atrophic mucosa or by the development of an infectious or ulcerative colitis. Progressive mental deterioration is apt to further limit the intake of food. Infection, particularly with Vincent's organisms or moniliae, is apt to occur in the mouth or esophagus, probably from failure of normal defense mechanisms. Finally, with extreme depletion of vitamins resulting from the combination of poor intake, poor absorption and inadequate utilization, such serious cerebral manifestations as hebetude, delirium, dementia or stupor or even the encephalopathic state ensue. At any stage in the progress of psychic and gastrointestinal symptoms patients may complain of paresthesias, particularly general formication, localized sensations of heat or burning and tingling of the palms and soles. Neuritic pain is frequent and may be associated with muscular weakness and depressed reflexes. In rare instances the picture of subacute combined sclerosis is seen. Photophobia, burning and itching of the eyes and dimness of vision are not uncommon.

Dermatitis is an essential part of the picture of pellagra and may occur at any stage. Various skin lesions are characteristic. There may be only symmetrical erythema of the dorsal surfaces of the hands or erythema may occur around the neck, over the upper sternum, the malar eminences and forehead. Frequently it is found on the elbows, forearms and feet. Rather commonly a vesicular or bullous dermatitis is superimposed on erythema. The genitalia, perineum and knees may be sites of dermatitis similar to that on the exposed surfaces; at times balanitis or vaginitis may be severe. In rare instances there is rapid necrosis of the skin over the dorsal surfaces of the hands, elbows, knees and feet; in such cases decubitus ulcers are apt to develop acutely. Dermatitis of the typical symmetrical distribution on the extremities often seems to follow trauma of any sort such as exposure to sunlight, radiant heat, friction or chemical irritants. It seems likely that perineal and genital lesions result from the irritation produced by decomposing urine and sebaceous secretions. The complete picture of pellagrous dermatitis has been seen to develop following intensive radiation of the mediastinum. It seems possible that dermatitis is always a result of some form of trauma to the skin in the presence of avitaminosis or that skin areas already "traumatized" may react with the production of dermatitis when a severe grade of avitaminosis is rapidly produced. Instead of the symmetrical erythematous and vesicular types of dermatitis, there may be simply thickening and pigmentation of the skin over the usual areas. Quite often there is localized follicular keratosis of the sebaceous glands of the forehead, nose, malar eminences and chin producing the "shark skin" eruption long associated with pellagra. Less often dermatitis is seborrheic and localized over the ears, malar eminences, alae nasi and chin. Not infrequently the lips are painful, red and desquamating with fissures at the commissures.

There are as yet no laboratory aids which are generally available for the diagnosis of avitaminoses of the B group. Much effort has been expended

on methods for quantitative determination of vitamins and coenzymes in the blood and urine and it is likely that simplified procedures will be developed which will be generally useful. At the present time such determinations are too complicated and time consuming to be of clinical importance. It seems likely that urinary excretion tests will be more helpful than determinations of the concentration of vitamins in the blood since the tissues seem to retain the vitamins until a really critical stage of depletion is present. The non-specific laboratory findings are worthy of mention. Anemia is present in some 84 per cent of cases; in the great majority (about 78 per cent) it is a typical hypochromic anemia undoubtedly due to inadequate intake or utilization of iron.[10] In a relatively small number of patients macrocytic and hyperchromic anemia is found. It is likely that a specific type of liver damage plays an important part in the genesis of this type of anemia since it is much more frequent in the so-called alcoholic pellagra than in the endemic disease due to prolonged dietary inadequacy. It has been shown that the liver in fatal endemic pellagra is rich in the erythrocyte maturing factor. This observation would suggest that the hepatic as well as the gastric defect in pellagra is different from that in pernicious anemia. Plasma proteins are commonly reduced at the expense of the albumin fraction. This finding is probably entirely non-specific and indicative only of inadequate protein intake. Gastric achlorhydria is found in some 80 per cent of patients with pellagra and, as mentioned previously, may be of significance as a cause of progressive failure to extract vitamins from food. Since the introduction of histamine there has been no significant variation in the incidence of achlorhydria so the older observations on the frequency of its occurrence are probably valid.

Because it has been suggested that excessive formation of porphyrin with chronic porphyrinemia might account for the relation between the typical pellagrous dermatitis and exposure to sunlight, considerable attention has been paid to the presence of porphyrin in the urine of pellagrins. When the urine of patients with pellagra or with evidences of nicotinic acid deficiency without dermatitis, is tested by the "first method" of Hans Fischer or the modification proposed by Beckh, Ellinger and Spies [12] a positive reaction is obtained in almost every instance. The procedure consists in strongly acidifying (pH4) an aliquot of the 24 hour specimen of urine and extracting it with two volumes of ether by shaking. The ether extract is washed twice with half volumes of distilled water, then extracted with a small amount (about 1/10 volume) of 25 per cent hydrochloric acid. The positive reaction is the development of a pink to purple color in the acid extract. It was thought at first that this color was due to the presence of coproporphyrin but Watson [13] and Dobriner and Rhoads [14] have shown that there is no relation between the amount of coproporphyrin present in the urine and the depth of color developed. Neither is there relation between the intensity of color and the clinical manifestations of pellagra. Visible color is due largely to urosein and while excessive amounts of copropor-

phyrin are excreted in certain instances of pellagra, this test does not detect it. Though the original purpose of the test has not been fulfilled it remains useful since it is positive only rarely in conditions other than the pellagrous syndrome. The pathological basis of the reaction remains obscure though it is thought to indicate impairment of liver function.

During the past three years it has become possible to separate the various symptoms and signs of at least most of the specific avitaminoses contributing to the syndrome of classic pellagra by therapeutic tests with pure vitamins. When patients presenting the complete picture are maintained on a basal diet extremely poor in all vitamins but adequately supplemented with vitamins A, C and D, the available members of the B group can be added singly in large amounts and valid conclusions drawn from the resulting effect on certain groups of morbid phenomena. As had been suspected, the paresthesias, neuritic pains, diminished tendon reflexes, edema and tachycardia so often seen in pellagra are relieved by the administration of thiamin chloride.[15, 16] Also, anorexia, flatulence and constipation often disappear during treatment with this vitamin.

When nicotinic acid is added, psychic manifestations of all grades are cured or greatly improved.[17, 18, 19, 20] In a number of instances, impairment of hearing has been greatly relieved.[9, 19] Appetite is often increased more strikingly than by thiamin; nausea and diarrhea are controlled promptly. The typical bright red, atrophic, frequently fissured or ulcerated tongue is blanched and often a rich growth of papillae is evident within 48 hours after treatment is begun. Stomatitis, esophagitis and lesions of the genitalia and rectal mucosa heal with equal rapidity even though secondary mycotic or spirillary infections are present. Typical dermatitis wherever located undergoes somewhat slower resolution but seldom requires more than ten days for healing. It is notable that seborrheic lesions are not cured. An apparently specific effect of nicotinic acid is the restoration of the acid secreting function of the gastric mucosa. This may follow a few weeks of treatment or may not occur until after many months of continuous administration of the vitamin. It is likely that this effect is important in the actual cure of pellagra since there is a direct relation between the incidence of relapse and the persistence of achlorhydria.[21]

During the first year of nicotinic acid therapy of pellagra it was noted that many patients whose glossitis, dermatitis and diarrhea were cured, retained certain lesions or acquired others as they were maintained on a basal diet supplemented with vitamins A, C, D and nicotinic acid. Seborrheic dermatitis of the face, the well known "shark-skin" follicular keratosis of the forehead, nose and malar eminences, redness and desquamation of the lips, fissures in the lips and at the commissures (the marginal stomatitis of Stannus[22]) persisted when present and developed in not a few. In a large number it was noted that from three to six weeks after the cure of pellagrous glossitis the tongue acquired a striking purplish-red or magenta color and that the newly grown papillae became flattened or mushroom-

shaped, giving the organ a finely pebbled appearance. At the same time there was redness of the buccal surfaces of the lips and often complaint of burning and soreness of the mouth and tongue. At first these phenomena were interpreted as signs of relapse of pellagra but in December of 1938, Sebrell and Butler [2] reported the experimental production of the majority of these lesions by a diet deficient in riboflavin and cure following the administration of this vitamin. More recently it has been shown that extensive "seborrheic" dermatitis [23,24] and various ocular symptoms and signs [18, 23, 24, 25] are manifestations of riboflavin deficiency. The ocular disturbances are of particular interest because of their wide prevalence. Photophobia, burning and itching of the eyes, ocular fatigue and dimness of vision not improved by correction of refractive errors and often, poor vision in dim light are complaints of pellagrins which are not relieved by thiamin or nicotinic acid but which disappear quickly during the administration of riboflavin. Patients with such complaints are found to have varying grades of vascularization of the cornea, at first superficial, later, interstitial and often associated with corneal opacities. This "nutritional keratitis" is rapidly cured by riboflavin in adequate doses.

Of more clinical importance than pellagra are the formes frustes of the avitaminoses of the B group which occur as definite clinical entities, usually without dermatitis and often without atrophic glossitis, diarrhea or the other classic manifestations of the syndrome. These are often precipitated by infection or by certain therapeutic efforts and in the past have been regarded as evidence of "toxic states." Not infrequently they represent the effect of severe acute vitamin deficiency superimposed upon a mild chronic polyavitaminosis. Alcoholism is a prominent cause of such conditions since the utilization of energy from alcohol involves the same coenzyme systems which are active in the metabolism of dextrose. The hypermetabolism of acute infections and hyperthyroidism are equally effective in producing exhaustion of the coenzymes. The therapeutic administration of large amounts of dextrose solutions by parenteral routes and the use of high carbohydrate diets and large amounts of insulin in the treatment of depleted diabetics [4] produce an analogous imbalance between derivation of energy from carbohydrate and replacement of vitamins necessary for its normal metabolism. The rapidity with which depletion is produced precludes the incidence of pronounced anatomical changes so that many features of the classic disease are lacking.

The picture of acute thiamin deficiency resulting from alcoholism is so well known that the incidence of neuritic pain, nerve and muscle tenderness, motor and reflex disturbances or edema and tachycardia without apparent cause immediately suggests this etiology. It is not so widely recognized that maintenance on parenterally administered solutions of dextrose may produce an analogous condition. After four or five days of such treatment edema, neuritic pain, tender nerve trunks and motor weakness are not infrequent. Edema occurring during prolonged venoclysis or repeated large

intravenous infusions of dextrose solutions has long been attributed to the use of physiologic saline solution as the solvent for dextrose and the large intake of water and sodium has been blamed for edema. Simple waterlogging from the introduction of excessive amounts of fluids has been the accepted explanation of edema occurring when no sodium chloride was present in the infusion fluid. While it is quite possible to produce edema by overloading the vascular apparatus with fluids, particularly in feeble individuals, this phenomenon seems relatively unusual. In our experience every instance of "waterlogging" associated with tachycardia, neuritic pain or tenderness of the extremities has shown prompt diuresis and relief of pain and tenderness as well as slowing of the heart when adequate doses of thiamin were given. Severe peripheral neuritis with quadriplegia may follow the combined use of large amounts of nicotinic acid and insulin in the treatment of postoperative psychosis.[6] Such therapeutic accidents emphasize the validity of the concept that "deficiency diseases" are essentially disturbances of the process of biological oxidation, the clinical manifestations depending on the particular stage of the utilization of energy from hexoses most affected. In the case of patients developing peripheral neuritis from large amounts of insulin and nicotinic acid, the mechanism seems obvious. Under the drive of large amounts of insulin, carbohydrate metabolism is tremendously increased, with an abundance of nicotinic acid (and probable reserves of riboflavin) the preliminary and intermediate stages of dehydrogenation proceed in the normal manner. In the final stage, decarboxylation of pyruvic acid fails because of lack of an adequate supply of diphosphothiamin (cocarboxylase) and the various clinical manifestations of beri-beri result.

Nicotinic acid deficiency without dermatitis is extremely common and frequently overlooked, even in localities where endemic pellagra is prevalent. It is highly probable that in a great majority of instances the symptoms and signs result from severe or almost total deprivation of the vitamin in individuals already in a borderline state of nutrition. Since the cerebral neurons seem to be particularly sensitive to the metabolic disturbances resulting from failure of coenzyme function, it is not surprising that psychic disorders predominate in this condition. Glossitis is frequent but often quite unlike that typical of pellagra. The red, rough, often partially coated tongue usually attributed to "toxic states" or to dehydration alone, the deeply fissured tongue or the geographic tongue have been seen so often in these patients that it seems justifiable to suspect that all such glossitides may be evidences of nicotinic acid deficiency. In many instances, however, the tongue is heavily coated, with neither papillary atrophy nor abnormal redness. Anorexia, nausea and vomiting are frequently the effects of avitaminosis as well as important contributors to its persistence and severity. Often, indeed usually, the relation of nicotinic acid deficiency to such common accompaniments of disease can be proved only by therapeutic test. Either psy-

chosis or glossitis may be the presenting manifestation; frequently they occur together.

It is common experience that many patients with infectious diseases such as pneumonia, erysipelas, osteomyelitis or any severe sepsis may develop glossitis, usually of the rough, red "toxic" type; occasionally the tongue is bright red and smooth. Mental confusion, delirium and "toxic psychoses" are almost equally frequent. It is customary in most hospitals to administer large amounts of dextrose solutions intravenously to patients with such conditions. Very often this treatment seems to aggravate the mental symptoms and the tongue and buccal mucosa become increasingly red sometimes with ulceration or the formation of pseudomembranes due to infection with moniliae or Vincent's organisms. Many times nausea and vomiting as well as soreness of the mouth and pharynx interfere with the taking of reasonably adequate nourishment. Even more often the combination of mental confusion or actual delirium and glossitis and stomatitis is seen in patients with complicated surgical conditions who from necessity are maintained for considerable periods by the parenteral administration of solutions of dextrose and physiologic saline solutions. All types of obstructive lesions of the gastrointestinal tract, acute cholecystitis, operations upon the stomach or bowel, all varieties of suppurative peritonitis and extensive infected wounds furnish frequent examples of this syndrome. It is seen very often too after emergency operations for urinary obstruction due to prostatism and here the type of operation seems to be unimportant. The factors which seem to be contributory to avitaminosis in these groups are fever, vomiting and the administration of large amounts of dextrose. Fever causes hypermetabolism with increased energy requirements; vomiting prevents the absorption of vitamins from any normal foodstuffs which may be taken. Glucose maintenance, though the only available method of alimentation in many instances, increases the utilization of coenzymes without furnishing any replacement.

A relatively infrequent but theoretically significant cause of avitaminosis is the use of a high carbohydrate diet and large amounts of insulin in the treatment of diabetics probably already in a borderline state of nutrition.[4] We have seen signs and symptoms of vitamin deficiency develop under these circumstances in five instances. The patients were all severely diabetic and living under such economic stress that it was not possible for them to procure a diet even reasonably adequate in protein and fat. They were hospitalized for regulation and in each instance the carbohydrate intake was raised to approximate that of the home diet available. This resulted in a ration of some 280 gm. carbohydrate, 70 gm. protein and 70 gm. of fat and required an increase of about 50 units of insulin per day above the former dose. (Insulin is available from relief agencies though proper food cannot be obtained.) In each case delirium occurred on the fourth or fifth day of the increased carbohydrate and insulin regime. In the first two, this was attributed to hypoglycemia until blood sugar determinations were made. Glossitis typical of nicotinic acid deficiency developed simultaneously with

psychosis in four patients; the fifth had the purplish granular tongue of ariboflavinosis. All five were free from mental symptoms on the second day of treatment with nicotinic acid, the one patient who showed evidence of riboflavin deficiency also, proceeded to develop cheilosis with fissures at the commissures of the lips. Such cases seem to furnish strong confirmation of the theory that the physiologic basis of symptoms in the "B" avitaminoses is the derivation of energy from carbohydrate in excess of the available supply of vitamins. With great increase in the utilization of carbohydrate in the presence of adequate amounts of insulin, these diabetics rapidly exhausted their scanty supplies of nicotinic acid and riboflavin and developed rather severe and acute evidences of deficiency.

Perhaps the most common and important manifestations of severe and relatively acute nicotinic acid deficiency are the profoundly psychotic and stuporous conditions described by Cleckley[19] and Jolliffe.[20] The clinical pattern is entirely variable; delusions, hallucinations, manic excitement as well as stupor and the encephalopathic state have been observed. Delirium tremens and post-alcoholic stupor have been seen to respond to massive doses of nicotinic acid and may tentatively be thought of as at least partly due to deficiency of this vitamin. The great majority of this severely psychotic group have shown no anatomical lesions of avitaminosis, glossitis and dermatitis being conspicuous by their rarity. This observation supports the suggestion of Jolliffe[20] that these states are due to total or subtotal deficiency produced with great rapidity so that there is not time for gross tissue changes to occur. A great many of our patients were elderly or senile with advanced arteriosclerosis. They presented a picture extremely familiar to all physicians practicing in general hospitals. Such patients are brought in unconscious; frequently they are known to have been living alone and in poor circumstances. Almost invariably the admitting diagnosis is uremia or some sort of cerebral accident. During the time required for completion of physical and laboratory examinations it is customary to give dextrose solutions intravenously to combat dehydration. Various tests show no evidence of severe renal insufficiency or of cerebral hemorrhage or thrombosis. Because such patients are not able to swallow, the extraoral administration of dextrose solutions is usually continued and after four or five days they die of bronchopneumonia. Treatment of such patients with nicotinic acid was tried rather empirically because there was frequent evidence of malnutrition and because the "red test" was positive in the urine. Rather surprisingly this high-mortality group was found to respond to the administration of nicotinic acid with rapid, often dramatic improvement. At least two of our patients presented the encephalopathic state described by Jolliffe[20] and, in his experience, due to chronic alcoholism. In this symptom complex, first emphasized by Bender and Schilder,[26] there is marked clouding of consciousness with variable cogwheel rigidities and uncontrollable grasping and sucking reflexes. Jolliffe was able to reduce the mortality in his large group of patients with this syndrome from 80 per cent in those treated with hy-

dration and supportive measures to 13.6 per cent in a series treated with large amounts of nicotinic acid. In our experience, 46 patients with stupor, delirium or encephalopathy had a mortality of 4.6 per cent as compared with 85 per cent of deaths in the years before nicotinic acid was used. In such patients it is entirely possible that the effect of nicotinic acid is twofold. We believe quite strongly that vitamin deficiency is the most important factor in the production of psychosis and its relief is a most important therapeutic objective. It is also probable that the vasodilator effect of nicotinic acid on arterioles results in a greatly increased supply of blood to the brain with much better supply of oxygen as well as pyridine nucleotides. This mechanism may apply to other organs and has been mentioned as a possible effect of arteriosclerosis in causing poor utilization of vitamins.

It must not be supposed that all stuporous or psychotic states of obscure etiology will respond to the administration of nicotinic acid or that any objection is raised to the use of dextrose solutions for hydration or parenteral nourishment. Reasonably thorough examination will reveal the common organic causes of delirium or stupor; when no such definite cause is evident, a therapeutic test with nicotinic acid is always justifiable. It is probably always wise to add nicotinic acid or sodium nicotinate to dextrose solutions when they are to be used for the prolonged hydration or nourishment of patients unable to swallow or retain food or fluids.

The amount of nicotinic acid required for the satisfactory treatment of the whole group of acute deficiencies is large. It has been our custom to give at least 600 mg. daily by mouth or through an indwelling stomach tube and 300 to 400 mg. by intramuscular or intravenous injection. Sodium nicotinate has been used almost exclusively for parenteral administration in amounts equivalent to the dose of nicotinic acid desired. When given intravenously it should be diluted with physiologic saline or with dextrose solution of desired strength to a concentration of about 0.05 per cent. (125 mg. of sodium nicotinate in 200 c.c. of diluent represents approximately this concentration.) For intramuscular injection a 10 per cent solution of sodium nicotinate has proved most satisfactory; the addition of 2 per cent of benzyl alcohol prevents pain at the site of injection. To avoid severe flushing reactions as well as waste of the vitamin from excretion it is advisable to limit single doses to 100 mg. of nicotinic acid or 125 mg. of the sodium salt.

The incidence of ariboflavinosis without definite clinical signs of other avitaminoses is high, suggesting that some conditioning factor yet unrecognized may prevent the utilization of this vitamin or create an unusual requirement for it. The studies of Steibeling [27] have indicated that there is widespread use of diets poor, if not actually inadequate, in riboflavin. In our experience, any or all of the factors which may cause nicotinic acid deficiency are effective in precipitating the signs of ariboflavinosis. These, as already noted, appear with great regularity in pellagrins treated with nicotinic acid alone and with no improvement in their diet. Many instances have been seen in persons using an apparently adequate diet and apparently free from

evident disease of the liver or gastrointestinal tract. The manifestations of acute riboflavin deficiency have not been adequately studied though there is reason to suspect that the state of collapse rapidly followed by death, which was formerly a common termination of severe pellagra, may be a manifestation of severe and possibly acute depletion.[32] Such patients show many symptoms similar to those observed by Sebrell and his collaborators [28, 29, 30] and by Street and Cowgill [31] in dogs with the experimental avitaminosis. It may be important too that the liver in fatal pellagra is almost invariably extensively infiltrated with fat, resembling the "yellow liver" described by Sebrell and others in ariboflavinosis of dogs.[10, 28, 30, 32]

Symptoms attributable to ariboflavinosis have already been mentioned. Lassitude and anorexia common to all the vitamin deficiencies are common; occasionally nausea is a prominent symptom. Ocular symptoms are exceedingly frequent and often precede oral lesions or dermatitis. Dimness of vision in poor light, blurred vision for distant objects, photophobia, "eye strain" and burning and itching of the eyes have been prominent complaints. These symptoms have been noted by previous observers. Spies, Vilter and Ashe [16] noted such visual disturbances in some 70 per cent of a large series of pellagrins and noted that in some instances they were relieved by riboflavin. Spies [33] in another communication was inclined to attribute these symptoms to vitamin A deficiency. Pock-Steen [25] observed all the above mentioned complaints in a group of 109 patients with sprue and leiodystonia. He also observed mydriasis, disturbances of accommodation and evidences of keratitis in some. Such symptoms and signs were relieved in 78 of his series by small amounts of riboflavin. As noted before, these complaints are not relieved by correction of errors of refraction and in the past have frequently been attributed to focal infection, "toxic states" or over use of the eyes.

The gross signs of riboflavin deficiency are quite irregular in the sequence of their appearance. The seborrheic lesions of the ears, alar portions of the nose, forehead or malar eminences may precede or follow characteristic cheilosis, fissuring of the commissures of the lips or glossitis. In our experience, the specific glossitis and redness of the buccal surfaces of the lips have seemed to precede other signs in the majority of instances. The filiform, keratotic comedones clustered in the naso-malar grooves or over the forehead, malar eminences, alae nasi or chin have seemed to be rather late lesions. Occasionally severe dermatitis of seborrheic type may involve the whole face and neck.

A superficial vascularizing keratitis has been found to be the earliest and most constant manifestation of ariboflavinosis,[24] having been seen before any other definite lesion was visible. Mydriasis is a relatively uncommon accompaniment but is marked in patients with severe photophobia and may be the cause of this symptom. Some patients show irregular deposits of pigment on the surface of the iris which are apparently related to riboflavin deficiency. The occurrence of ocular lesions in human ariboflavinosis is not

surprising since it is such a prominent part of the picture in the experimental avitaminosis in rats. Day and his collaborators,[34, 35] O'Brien,[36] Bourne and Pyke [37] and others have noted corneal opacities which cleared under treatment with riboflavin. Bessey and Wolbach [38] and Eckardt and Johnson [39] emphasized keratitis as an almost constant lesion. Bessey and Wolbach, using the slit lamp, were able to follow the development of keratitis during periods of experimental riboflavin deficiency in their rats and to observe resolution after treatment. Their report suggested slit lamp inspection as a method of early diagnosis in human beings.

Using the slit lamp, the earliest change observed in human subjects has been marked engorgement and proliferation of the limbic plexus with obliteration of the normal, narrow avascular zone between the extreme margin of the sclera and the cornea. Often each scleral digitation comes to be outlined by a large capillary loop. Recognition of this condition as abnormal followed the observation that such overfilling of the limbic plexus rapidly disappeared following the administration of riboflavin. If the deficiency is allowed to persist, fine capillaries sprout from the apices of the loops outlining the scleral digitations and invade the cornea just beneath the epithelium. These centripetally directed vessels soon anastomose to form a secondary arcade of capillary loops from which more capillaries sprout. This process may be repeated until an extensive superficial plexus is formed. Using retroillumination it is possible to see the newly formed capillaries before they become filled. Usually by the time secondary invading loops are formed, some capillaries arising from the limbic plexus invade the *substantia propria.* The process of corneal vascularization has not been followed further than this stage in patients but fully developed keratitis has been seen in which there were very large superficial and interstitial vessels with a dense plexus of fine capillaries throughout the *substantia propria.* Only a few vessels seem to strike deeply and run centripetally just inside Descemet's membrane. This absence of a dense posterior plexus seems to differentiate dietary keratitis from that occurring in syphilis where a posterior plexus is prominent. Diffuse superficial opacities have been seen in many patients with ariboflavinosis and interstitial opacities in a few. In two instances dense scars, apparently from old ulcers, were present. If the process in human beings is similar to that observed by Bessey and Wolbach in rats, the superficial and interstitial opacities are due to leukocytic infiltration of the subepithelial and deeper areas respectively. Posterior keratitic deposits have not been observed. Pigmentary changes in the iris are interesting though their significance is not yet understood. Many patients with gray irises have shown brown pigment spots not yet differentiated from "hazel spots" which disintegrated and disappeared during the administration of riboflavin. A number of those with brown irises showed a peculiar shaggy pigmentation of the entire anterior iridic membrane which obscured the normal architecture. This also was seen to disappear during treatment.

The specificity of these corneal and iridic changes as signs of aribo-

flavinosis seems to have been proved by their rapid resolution during administration of the vitamin. The amount necessary to produce rapid emptying of invading vessels and disappearance of opacities has varied from 3 to 15 mg. per day. Patients with early or slight vascular keratitis showed rapid improvement of symptoms and emptying of newly formed capillaries in the cornea with the smaller dose. Most patients were given 5 mg. daily; only those with severe keratitis received 15 mg. Emptying of very recently formed capillaries was observed after the ingestion of as little as 4 mg. of riboflavin; most patients required from 12 to 25 mg. before definite improvement was visible. Opacities tended to be slower in disappearing, seldom showing definite change before the sixth day of treatment. The time required for complete emptying of corneal vessels and clearing of opacities varied from six to fifteen days. Symptoms were quite regularly relieved by the fourth day of treatment. In a number of instances, treatment was withheld after maximal improvement had been attained. In no case was there failure of relapse. The time required for experimental relapse varied from two to eighteen days. Complete disappearance of newly formed corneal vessels has not been observed, though no case has been followed for more than seven months. While entirely empty of blood they remain visible by direct illumination as fine refractile lines and by retroillumination as coarser gray streaks. Spontaneous relapse during treatment has occurred, usually as a result of seemingly obvious causes. Fever from intercurrent infection, nausea and diarrhea from food poisoning and the incidence of pregnancy have seemed to be particularly potent. A few patients have relapsed without evident cause but have promptly been cured by increase in the dose of riboflavin. An interesting and as yet obscure phenomenon is the fact that relapse following withdrawal of the vitamin constantly results in a much more severe keratitis than that present before treatment was begun.

Several interesting and perhaps important observations have been made. Mydriasis occurring in patients with ariboflavinosis is quite constantly abolished while the vitamin is administered. The mechanism of this mydriasis is as yet unexplained. The pigmentary changes of the iris, while probably due to migration of melanophores to the anterior surface of the iris, are not regularly associated with classical iritis or evidence of congestion of the intrinsic plexus. More intriguing than any other phase of the experiment is the fact that several cases of "typical" syphilitic interstitial keratitis which showed no improvement or had come to a standstill after intensive antisyphilitic therapy have responded to the administration of riboflavin by relatively rapid emptying of all corneal vessels, the superficial and interstitial plexuses being the first to empty, the posterior requiring from five to 15 weeks of treatment to become free of blood. Dense anterior and interstitial opacities have cleared so that patients whose vision was less than 5/200 have attained as much as 15/20. Relief of photophobia in these cases has been remarkable; patients who wept constantly in the dark have been able to

endure full sunlight or the glare of photographic lamps after the ingestion of 15 to 30 mg. of riboflavin. It would seem that riboflavin may prove a valuable adjunct to the treatment of syphilitic keratitis though the mechanism of its action in this condition is not clear.

The rationale of riboflavin deficiency in the production of ocular symptoms and signs has been suggested by Bessey and Wolbach[38] and Kimble and Gordon.[40] The symptom, poor vision in dim light, may well be attributed to faulty utilization of vitamin A, which has been shown to occur in the absence of adequate supply of riboflavin. Photophobia is probably the effect of spastic mydriasis, for which no mechanism has been suggested. Poor distant vision probably depends on accommodation defect which is common in ariboflavinosis but is as yet unexplained. The mechanism of vascularizing keratitis is fairly obvious. Bessey and Wolbach suggested that in riboflavin deficiency the cells of the cornea lack enough of the vitamin to secure the transport of oxygen from the air through the cells of the epithelial layer to those of the *substantia propria.* In response to anoxemia of the *substantia propria,* capillaries spring from the limbic plexus to furnish oxygen transport directly from erythrocytes to the deeper layers of the cornea.

In the treatment of ariboflavinosis it is important to note that relatively large amounts of the vitamin are necessary. Steibeling[27] estimated that about 2 mg. is the normal daily adult requirement. We have found that 3 mg. is probably a minimal therapeutic dose and that most patients require 5 mg. and some as much as 15 mg. for rapid improvement. For specific effect it is necessary to use the pure synthetic vitamin since it is almost impossible to secure adequate intake otherwise. No satisfactory preparation for injection is available and it seems likely that absorption and utilization of riboflavin is much more likely to be diminished by conditioning factors than is that of any of the other B group vitamins. It is important also to protect all preparations of riboflavin from light since even short exposure may cause reduction to the inactive leukoflavin.

In conclusion it seems necessary to emphasize the fact that an adequate diet is the most important therapeutic measure in all avitaminoses. Regardless of the administration of pure vitamins or mixtures of them, sufficient amounts of protein and fat are essential to health and minerals must be supplied. It is particularly important to refrain from treating presenting symptoms due to a single predominating avitaminosis with large amounts of the specific vitamin. This procedure is almost certain to precipitate the manifestations of coincident subclinical deficiencies of other members of the group.

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FUNDAMENTAL PRINCIPLES IN THE ADJUSTMENT REACTIONS OF THE ORGANISM TO ANOXIA *

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A STUDY of the effects of anoxia on the human organism and on laboratory animals is of particular value to physiology and medicine because it lends itself well to demonstrating the interrelation of various organ systems in the body. This aspect of the problem will be stressed in the following discussions as well as some important clinical implications. Finally an attempt will be made to show which characteristics of the central nervous system are ultimately responsible for the adjustment reactions occurring in anoxia.

It is well known that under the influence of anoxia as induced by the breathing of suitable oxygen-nitrogen gas mixtures, the respiratory volume increases and the blood pressure is raised. Both reactions greatly contribute to an improvement of the oxygenation of the tissues and particularly of the brain. It is of great interest to show the interrelation of these two reactions. Numerous experiments conducted on dogs anesthetized with chloralosane have shown that both respiratory and blood pressure responses increase with decreasing concentration of oxygen in the inhaled air (Gellhorn and Pollack [21]). Two different types of response can easily be distinguished. The first is characterized by a marked respiratory response and little or no alteration in the blood pressure; the other shows a small respiratory response and pronounced blood pressure effects. Figure 1 illustrates these two types. In both experiments 11 per cent oxygen was inhaled for five minutes. The blood pressure was recorded from the femoral artery and the respiratory

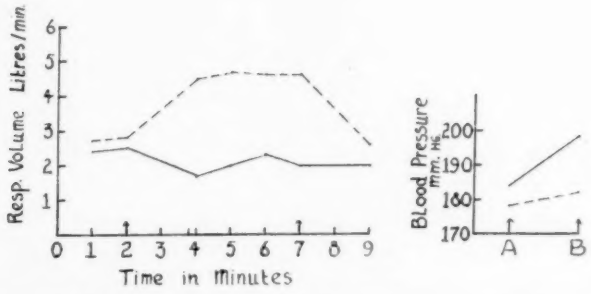

FIG. 1. Influence of inhalation of 11 per cent oxygen on blood pressure and respiration of two dogs narcotized with chloralosane 100 mg./kg. intravenously. Seven per cent O_2 administered between the second and seventh minutes. On the right side changes in blood pressure: A: Blood pressure before anoxia; B: maximal rise of blood pressure during anoxia.

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volume was determined at intervals of one minute. Whereas the blood pressure rises 14 mm. in the experiment in which anoxia does not increase respiration, it rose only 4 mm. in the other experiment in which a marked respiratory response occurred.

It is very probable that the different reactions were due to the fact that the respiratory center was more depressed in one case than in the other although the anesthesia was the same in both cases. These observations make it likely that the respiratory response is the primary reaction of the organism to anoxia, and that only if this reaction is impeded or if the degree of anoxia is too severe to be adjusted by the respiratory response alone, the vasomotor reaction occurs leading to an improved circulation of brain and heart in proportion to the rise in blood pressure. Such an interpretation is supported by the observation that with increasing severity of anoxia the blood pressure reaction comes into action to an increasing degree. It is further illustrated by experiments in which in the same animal, the blood pressure response is studied under conditions of artificial respiration (pneumothorax).

Figure 2 shows how greatly the blood pressure rises on inhalation of 11 per cent oxygen after the respiratory adjustment has been eliminated by a pneumothorax. There was practically no change in blood pressure during anoxia when the respiratory adjustment was permitted to occur. When, however, a pneumothorax was made the blood pressure rose 35 mm. Hg in response to 11 per cent oxygen.[21]

Figure 3 illustrates the validity of our assumptions in an experiment in which the respiratory response to a mild anoxia was weak and consequently some rise in blood pressure occurred during inhalation of 11 per cent oxygen. Again the blood pressure reaction is distinctly increased after pneumothorax. Particularly interesting is the third record of figure 3 which was obtained when the respiratory minute volume under conditions of pneumothorax was reduced by nearly one half. The blood pressure level remained unchanged as long as air was inhaled, but when 11 per cent oxygen was administered the blood pressure rise was greatly increased over and above the reaction observed in the same animal when the respiratory volume was adjusted at a higher level. Moreover, marked signs of vagal stimulation occurred.

The blood pressure reaction to anoxia is also greatly modified under conditions which involve either anemia of the brain or of the whole organism. A certain degree of brain anemia may easily be established by temporary clamping of one or more of the main arteries to the brain.[21] Such an experiment is illustrated in figure 4 in which at the beginning and at the end of the record, the blood pressure reaction to the inhalation of 4.5 per cent oxygen is shown, whereas in the two intervening experiments the effect of inhalation of 4.5 per cent oxygen on the blood pressure was studied under conditions of restricted brain circulation. In the first case both carotid arteries were clamped, in the second experiment both vertebral arteries were temporarily ligated. It is clearly seen that the temporary elimination of the

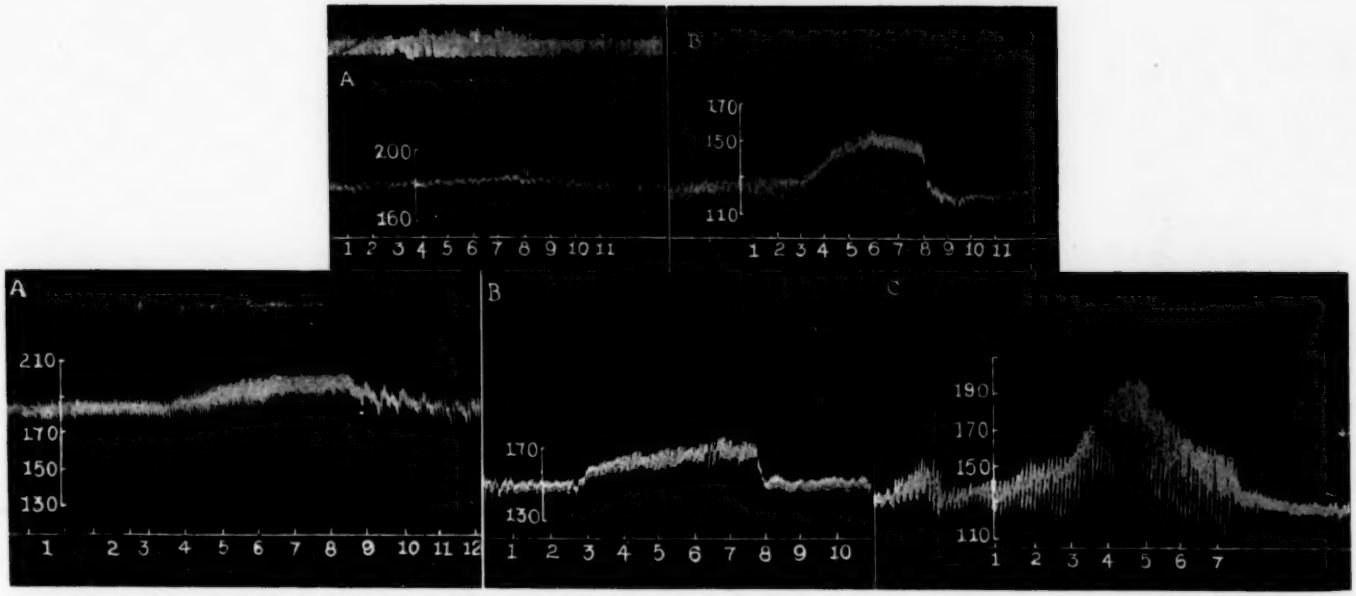

FIG. 2. *Above.* Dog 20. 1–10–40. 10.5 kg. 70 mg./kg. chloralosane. Influence of inhalation of 11 per cent oxygen on the blood pressure (lower curve). A: natural respiration (upper curve), 11 per cent oxygen administered between 3 and 8. B: Pneumothorax; Respiratory volume—2.87 1/min.; 11 per cent oxygen between 3–8.

FIG. 3. *Below.* Dog 14. 12–21–39. 11.7 kg. 100 mg./kg. chloralosane intravenously.
A. Natural respiration. Eleven per cent oxygen administered for 5 min. from 3 to 8.
B. Pneumothorax—11 per cent oxygen from 3 to 8. Respiratory minute volume kept at 2.5 1.
C. As in B, but respiratory minute volume kept at 1.38 1.

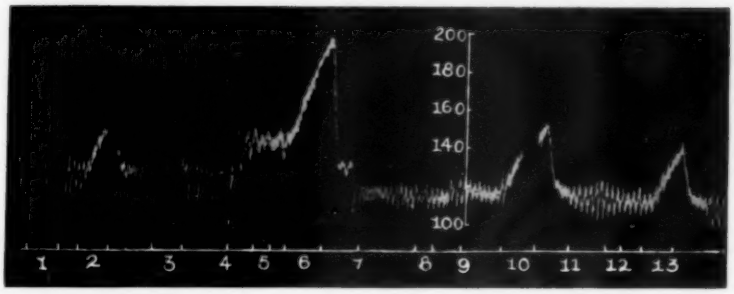

FIG. 4. Dog 7. 11–29–39. 8.4 kg. 100 mg./kg. chloralosane intravenously. Influence of temporary clamping of carotid and vertebral arteries on the blood pressure response to inhalation of 4.5 per cent oxygen.

2—4.5 per cent O_2 for 60 seconds.
4—clamping of both carotid arteries below the bifurcation.
6—4.5 per cent O_2 for 60 seconds.
7—release carotids.
9—clamping of both vertebrals.
10—4.5 per cent O_2 for 60 seconds.
11—release vertebrals.
13—4.5 per cent O_2 for 60 seconds.

blood flow of the carotid arteries greatly intensifies the rise in blood pressure induced by the inhalation of 4.5 per cent oxygen. This may in part be due to the fact that after bilateral clamping of the carotid arteries the compensatory blood flow through the brain made possible by dilation of the cerebral vessels (Cobb [4] and Fremont-Smith, Wolff and Lennox [31] and others) cannot take place to the same degree in response to anoxia as it does under conditions of normal brain circulation. Consequently a more marked anoxia of the vasomotor system results which in conjunction with the stimulation of the chemoreceptor apparatus leads to an increased blood pressure. The elimination of the pressor receptors of the carotid sinus by the clamping of the common carotid arteries may also play a part in this reaction and this interpretation is supported by the observation that vagotomized animals respond with a still greater rise in blood pressure when subjected to anoxia under conditions of restricted brain circulation.

After temporary ligation of the vertebral arteries the blood pressure rise to anoxia is only slightly greater than is observed under control conditions, and in some cases the elimination of the vertebral circulation does not appreciably alter the blood pressure response.[21]

Whatever the ultimate explanation of the mechanism may be whereby the blood pressure response to anoxia is altered by reducing the blood flow through the brain it is interesting to show that moderate restrictions in brain circulation (clamping of one carotid artery or of one or two vertebral arteries) may so adequately be compensated by increased rate of blood flow (Rein [29]) that no change in the blood pressure response to anoxia is seen when compared with that observed when all arteries are open. If, however, both carotid arteries are clamped, a more adequate circulation through the brain is secured by the increased blood pressure response to anoxia.

Brief reference may be made at this point to the observation of Cushing [5] who found that if the intracranial pressure is raised to the level of the arterial blood pressure a vasomotor reaction occurs by which the blood pressure is raised above its normal level, and consequently also above the intracranial pressure. It is clear that such a reaction will lead to a restoration of circulation in the brain which had been interrupted by the increased intracranial pressure. Yesinick and Gellhorn [32] observed that this reaction is greatly increased during anoxia. Figure 5 illustrates this condition. The observations of Yesinick and Gellhorn make it probable that the vasomotor reaction occurring on increased intracranial pressure is due to an asphyctic stimulation of the medullary centers. It therefore may be said that a reduc-

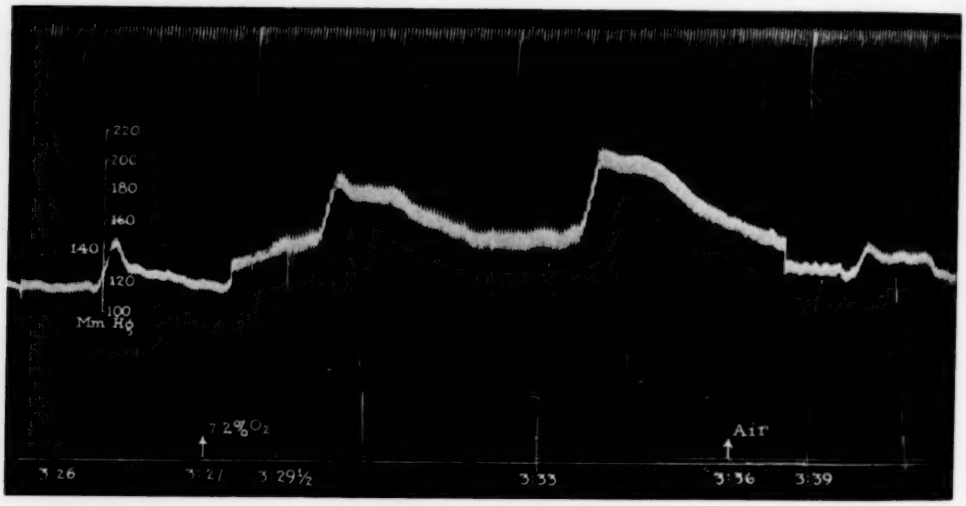

FIG. 5. Influence of anoxia on the blood pressure response to increased intracranial pressure.
Upper curve: Artificial respiration.
Middle curve: Blood pressure.
Lower curve: Intracranial pressure.
The first and last record show the rise of blood pressure on increasing the intracranial pressure to the blood pressure level under control conditions. The second and third curves show the effect of anoxia induced by inhalation of 7.2 per cent oxygen on this reaction.

tion in the blood supply affecting the whole brain (experiments with restricted brain circulation) aggravates the blood pressure response to anoxia. Similarly, it is found that anoxia intensifies the effects of local anemia of the brain stem (experiments with increased intracranial pressure). Not only local anemia acts in this way, but general anemia also sensitizes the medullary centers to anoxia. Figure 6 shows that after successive bleedings both blood pressure and respiratory responses greatly increase during inhalation of 7 per cent oxygen. Here again is shown that a marked alteration in blood pressure response to anoxia is seen only after considerable loss of blood although the respiratory response increases quite markedly to lesser degrees of hemorrhage.[21]

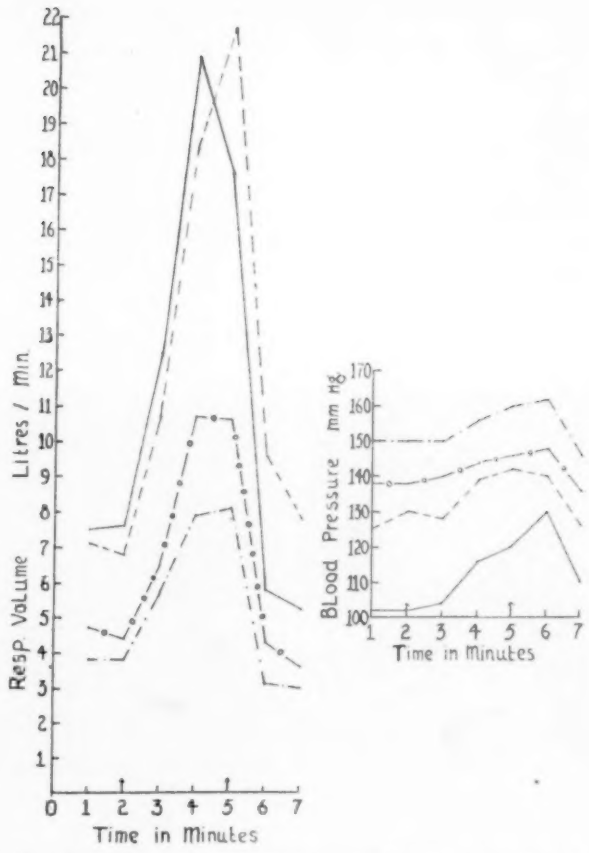

FIG. 6. Dog 43. 4–19–40. 12.5 kg.; 70 mg. chloralosane intravenously. Effect of progressive hemorrhage on the reaction of blood pressure and respiration to the inhalation of 7 per cent oxygen for 3 min. (between the arrows at 2 and 5).

– · – · – Prior to the bleeding
– o – o – After loss of 9 per cent of calculated blood vol.
– – – – – After loss of 13 per cent of calculated blood vol.
——— After loss of 28.5 per cent of calculated blood vol.

The experiments which were cited illustrate under a variety of conditions three phenomena. They show

1. That the respiratory response to anoxia is a finer indicator of this condition than is the blood pressure.
2. That the blood pressure response to anoxia depends, other conditions being equal, on the degree of the respiratory response.
3. That both respiratory and circulatory responses to anoxia increase in conditions involving a reduction of blood supply to the medulla oblongata or to the whole brain. Similar effects are produced by a general anemia induced by bleeding.

As to the nature of the respiratory and blood pressure response only a

brief statement can be made. Heymans [25] and many other authors have shown that the increased respiratory response to anoxia is due to the action of the diminished oxygen tension of the blood on the chemoreceptors in the sino-aortic area since after elimination of the chemoreceptors respiration gradually fails. The organization of the vasomotor center is quite similar. Gellhorn and Lambert [20] showed that even under conditions of artificial respiration the blood pressure falls in anoxia after the buffer nerves have been eliminated, whereas in their presence the blood pressure rises on inhalation of oxygen-nitrogen mixtures (figure 7). This result is so typical in the dog that the fall in blood pressure during anoxia may be used as a test indicating complete removal of carotid sinus and depressor nerves.*

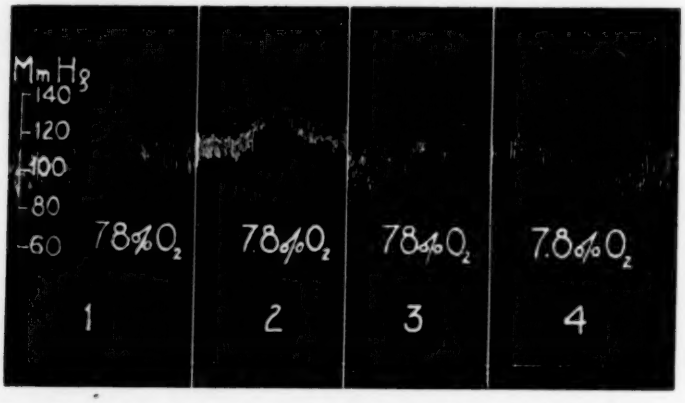

Fig. 7. The effect of vagotomy alone and vagotomy plus carotid sinus denervation on the blood pressure reaction of a dog to oxygen deficiency. Sodium amytal, 55 mg. per kilo; artificial respiration. Upper tracing represents blood pressure; lower tracing, signal indicating the period of administration of the gas mixtures. No. 1: Intact animal: 7.8 per cent oxygen administered for a period of 60 seconds. (Between 1 and 2, the right vagus nerve was cut in the neck.) No. 2: 7.8 per cent oxygen administered for a period of 60 seconds. (Between 2 and 3, the left vagus nerve was cut in the neck.) No. 3: 7.8 per cent oxygen administered for a period of 60 seconds. (Between 3 and 4, the carotid sinuses were denervated.) No. 4: 7.8 per cent oxygen administered for a period of 60 seconds. (From E. Gellhorn and E. Lambert.[20])

The regulatory processes which are evoked by anoxia are gradually weakened by the loss of carbon dioxide which accompanies the increased respiratory ventilation. It is therefore of considerable interest to call attention to the fact that in the human organism, anoxia may frequently be accompanied by an increased carbon dioxide tension in the blood as, for instance, in conditions of muscular exercise, or it may gradually lead to an accumulation of carbon dioxide if the circulatory adjustment breaks down. Thus it has been found that in the early stages of pneumonia a pure anoxia prevails, but at later stages of this disease due to circulatory impairment, the carbon dioxide tension in the blood rises (Meakins and Davis [26]).

It seems to be of importance to distinguish between anoxia which is ac-

* Concerning details and bibliography cf. Gellhorn and Lambert.

companied by a fall in the carbon dioxide tension of the blood due to the compensatory increase in respiration and the condition of asphyxia which is characterized by a fall in oxygen and a rise in the carbon dioxide tension of the blood.

Asphyxia produced by clamping of the trachea causes such a rapid fall in oxygen and marked rise in carbon dioxide tension that after a brief excitatory state characterized by a rise in blood pressure and increased respiration both respiration and circulation fail. If, however, carbon dioxide is being accumulated only to a lesser degree thereby preventing the harmful effects of acapnia which ordinarily accompanies anoxia the adjustment reactions to anoxia are greatly strengthened. This can be shown in the human by studying the influence of inhaling 8.5 per cent oxygen with or without the presence of carbon dioxide. If the experiment is conducted in erect posture the systolic blood pressure falls within a few minutes and collapse may ensue.[11] But the same subject may easily tolerate this low oxygen concentration when the ill effects of acapnia are prevented by carbon dioxide.

On the basis of such experiments moderate asphyxia may be considered a final attempt of the organism to rid itself of the anoxia. This may be accomplished by the fact that the blood pressure rise in response to a given oxygen tension is markedly enhanced by even small amounts of carbon dioxide which in itself has no effect on the blood pressure (Gellhorn and Lambert,[20] Raab [27]). The loss in muscle tone which accompanies anoxia and which is responsible for an insufficient venous return to the heart may be offset by small amounts of carbon dioxide. This was shown (Gellhorn and Hamilton [16]) by employing the direct method of measuring muscle tone by which Henderson [24] showed that carbon dioxide increases the muscle tone. The respiratory response to a given oxygen tension is also increased in the presence of small concentrations of carbon dioxide in inhaled air (Dill [6]).

Finally it is known that the sympathetico-adrenal system which so greatly aids in the improvement of the circulation of the brain and heart is called into action to a much greater extent under conditions of asphyxia than in an anoxia of the same degree. This can be demonstrated by a comparative study of the influence of anoxia and asphyxia on the blood sugar of unanesthetized rabbits.[20a] Figure 8 shows that the blood sugar rises much more on inhalation of 7 per cent oxygen plus 4.5 per cent carbon dioxide than on inhalation of 7 per cent oxygen alone in spite of the fact that carbon dioxide itself does not cause any hyperglycemia. These experiments seem to indicate that the most effective treatment of anoxia would consist of the administration of carbon dioxide in oxygen (cf. Henderson [24]) but only direct clinical studies can decide questions of therapy.

The greater reaction of the blood pressure and respiration and of the sympathetico-adrenal system to anoxia in the presence of carbon dioxide makes it highly probable that functions of the brain may withstand anoxia better when it is not accompanied by any decrease in the carbon dioxide tension in the blood. It seems rather probable that even slight increases in the

carbon dioxide tension of the blood may improve brain circulation in anoxia. Studies on various functions of the brain performed in humans and laboratory animals under conditions in which gases low in oxygen are inhaled either with or without some excess of carbon dioxide show indeed that brain functions are much better preserved when acapnia is avoided.[8, 9, 10, 12, 13, 18, 19]

The effects resulting from inhaling 8.5 per cent oxygen with and without 3 per cent carbon dioxide are most marked when the highest cortical functions are investigated. It was seen that whereas during inhalation of 8.5 per cent oxygen mental functions involved in the addition of two digits are markedly impaired as shown by the increase in the number of errors, and in the time necessary to perform these operations, the same degree of anoxia

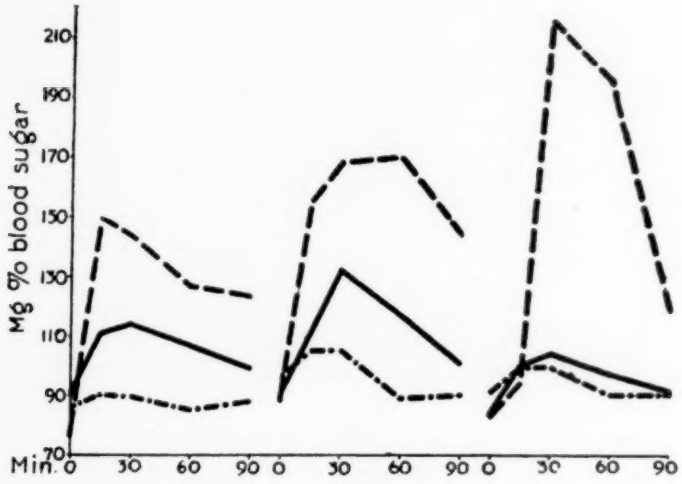

FIG. 8. The influence of CO_2 and oxygen lack on the blood sugar of rabbits. The gases were administered from Douglas bags for 90 minutes.

Abscissa: Time in minutes.
Ordinate: Blood sugar in mg. per cent.
———— During inhalation of 7 per cent O_2.
- - - - - - - - - During inhalation of 5.4 per cent CO_2.
– – – – – – – – – During inhalation of 7 per cent O_2 + 5.4 per cent CO_2.

(From E. Gellhorn and A. Packer, Proc. Soc. Exper. Biol and Med., 1939, xlii, 475.)

remained ineffective when 3 per cent carbon dioxide was inhaled at the same time. Similarly it was found that memory suffered much in anoxia although practically no deficiency was found when the anoxia test was carried out in the presence of 3 per cent carbon dioxide.[13] Pathological deviations were revealed in association tests in anoxia but were absent when 8.5 per cent oxygen plus 3 per cent carbon dioxide were inhaled. Disturbances in mood were frequently observed during anoxia but failed to appear when acapnia was prevented by the simultaneous inhalation of carbon dioxide.[15]

A number of sensory tests were carried out and showed similar results. Visual function was impaired in anoxia but the presence of carbon dioxide

prevented its occurrence.[9] Brain stem reflexes induced by caloric stimulation were investigated in the rabbit and it was found [22] that the decrease in intensity of nystagmic movements observed in anoxia failed to appear when the rabbits inhaled the same percentage of oxygen in the presence of 4 to 5 per cent carbon dioxide.[22] Disturbances in muscular coördination progressing with increasing duration of the anoxia period are best revealed in writing (figure 9). They are in sharp contrast with the results obtained when the same gas mixture was inhaled in the presence of 3 per cent carbon dioxide.[13]

These experiments prove that on account of the synergistic action of oxygen lack and carbon dioxide on respiratory and autonomic functions the

FIG. 9. Writing in an association test. (From E. Gellhorn, Am. Jr. Psychiat., 1937, xciii, 1413.) *9a:* The influence of the inhalation of 8½ per cent oxygen plus 3 per cent carbon dioxide. *9b:* The influence of the inhalation of 8½ per cent oxygen.

brain circulation is restored to such a degree as to offset completely, within certain limits, the effects of oxygen lack on the brain.

The reactions described thus far tend to improve the oxygenation of the tissues by increasing the oxygen tension in the alveolar air and by improving circulation in brain and heart. Many other subsidiary reactions take place which work in the same direction. They cannot be discussed here, but the contraction of the spleen increasing the number of circulating red blood cells (Barcroft [1]), the opening of heretofore closed alveoli (Verzàr [30]), the more rapid unloading of the oxygen in the erythrocytes in the presence of increased carbon dioxide concentrations such as may occur in asphyxia may be men-

tioned. All these reactions improve the oxygenation of the tissues by facilitating transportation of oxygen to the tissues in anoxia.

These reactions are effectively supplemented by others which tend to reduce the oxygen demands of the tissues. It is well known that the metabolism of the organs depends on the temperature. A lowering in the body temperature would be a most effective means of reducing oxygen demands and thereby allowing the organism to continue its function under conditions of diminished oxygen supply. Such a reaction indeed occurs (Behague,[2] Chevillard and Mayer [2a]) and is particularly well established in small animals with a relatively large surface area of the body (Gellhorn and Janus [17]). It is interesting to note that in the presence of carbon dioxide, the fall in body temperature induced by anoxia is greatly increased, as figure 10 indi-

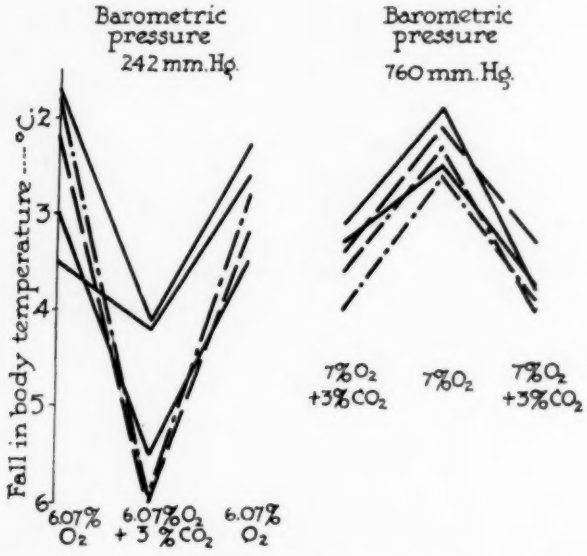

FIG. 10. The influence of a reduction in the O_2-tension in the inhaled air with and without 3 per cent CO_2 on the body temperature of the rat. Duration of each experiment 55 minutes.

Ordinate: Fall in body temperature in degrees C.

Abscissa: Composition of the gas mixtures. In the left curve the reduction in O_2-tension was obtained by reduction in barometric pressure, whereas in the experiments represented by the right curve the barometric pressure was normal and the O_2 concentration was obtained by dilution with nitrogen. (From E. Gellhorn, Am. Jr. Physiol., 1937, cxx, 190.)

cates.[14] This would mean that the conversion of anoxia into asphyxia improves not only the conditions for the transportation of oxygen to the tissues but also reduces more effectively the tissue metabolism than is accomplished by anoxia alone. Observations of Rein [28] showing that inhalation of carbon dioxide reduces the basal metabolism in the human in spite of increased respiratory activity seem to support this conclusion.

It is well known that anoxia and carbon dioxide depress somatic excit-

ability at cortical, subcortical and spinal levels, but the same factors stimulate respiratory and vasomotor centers, anoxia by its action on the chemoreceptors and carbon dioxide also directly. The possible causes of this discrepancy were investigated in order to find a clue to the mechanisms underlying adjustment reactions in anoxia. For this purpose experiments were performed which allow one to compare autonomic and somatic reflexes at approximately the same level of the central nervous system.

As a medullary reflex, the linguo-maxillary reflex was chosen. It is elicited by stimulating the endings of the lingual nerve in the tongue with condenser discharges and recording the contractions of the digastric muscle which is innervated by the motor branch of the trigeminal nerve. Respiration and blood pressure were recorded at the same time. Most of the experiments were conducted on cats anesthetized with chloralosane which maintains well the reflexes mediated by the carotid sinus and arch of the aorta. It was found that anoxia decreases reversibly somatic excitability as measured by the linguo-maxillary reflex (Greenberg and Gellhorn [23]). At the same time respiration is markedly increased and the blood pressure rises. Similarly it is found that asphyxia induced by clamping of the trachea inhibits the linguo-maxillary reflex while stimulating the respiration and blood pressure. The effects of anoxia and carbon dioxide on the somatic reflex are not altered by denervation of the carotid sinus and bilateral vagotomy although it is well known that the blood pressure and respiratory response is depressed in the "denervated" animal in anoxia. The experiments seem to point out that the chemoreceptors of the buffer nerves do not exert an excitatory influence on the somatic but only on the autonomic and respiratory centers.

Similar results were obtained in cats in which the hypothalamus was stimulated and the contraction of the nictitating membrane was recorded (Carlson,[3] Darrow and Gellhorn). In a number of experiments central stimulation of the hypothalamus and peripheral stimulation of the cephalad end of the cut cervical sympathetic were performed in order to evaluate the peripheral and central effects of anoxia. It was observed that under these conditions only the central excitability greatly increased. It is interesting to point out that the movements of the extremities which ordinarily accompany hypothalamic stimulation gradually disappear under anoxia while the contraction of the nictitating membrane increases. This seems to indicate that anoxia decreases somatic but increases autonomic excitability also at the hypothalamic level. Moreover, it was found that during anoxia the threshold for somatic movements is markedly increased.

Two explanations seem to be possible for the differential effects of anoxia on somatic and autonomic excitability. First that the somatic centers are more sensitive to these agents than are autonomic centers. Second that the effects presented are not the results of a direct alteration of hypothalamic or medullary excitability but due to release from higher inhibitory centers. In this case it must be assumed that not the same degree of inhibition is exerted

on somatic and autonomic centers. Experiments on decerebrate cats seem to refute this assumption since in these animals also anoxia causes an increase in respiration and raises the blood pressure while decreasing the linguomaxillary reflex.

These investigations seem to indicate that the autonomic centers are less sensitive to anoxia than are the somatic centers. They may therefore respond to anoxia with a heightened excitability whereas somatic centers show this effect only temporarily and pass then into a phase of diminished excitability. This difference in excitability accounts for the adjustment reactions occurring under conditions of anoxia and asphyxia. It is interesting to note that the respiratory center shows functionally a greater similarity to sympathetic than to other somatic centers.

Summary

Adjustment reactions to anoxia were studied in humans and laboratory animals with emphasis on respiration and circulation. The results were as follows:

1. It was found that with decreasing oxygen concentration in the inhaled air, both respiratory volume and blood pressure increased progressively.

The blood pressure response is closely related to the respiratory response, inasmuch as in mild degrees of anoxia a respiratory response occurs without alteration in blood pressure. If, however, the respiratory response is poor or artificially curtailed by pneumothorax the blood pressure rises markedly in proportion to the reduction in respiration.

2. The blood pressure rise to a given degree of anoxia is markedly increased when the blood flow through the brain is diminished by temporarily clamping either the carotid or the vertebral arteries. The occlusion of the former is far more effective than that of the latter, which may be due not only to the greater amount of blood supply by the carotid arteries as compared with the vertebrals, but also to the elimination of the carotid sinus receptors in the experiment involving occlusion below the bifurcation. Anemia of the medulla induced by increased intracranial pressure causes a greater increase in blood pressure in anoxia than under control conditions.

Finally it was found that general anemia induced by progressive bleeding increases blood pressure and respiratory response to anoxia, although the blood pressure level was not significantly altered by the withdrawal of blood.

3. If the effects of acapnia which ordinarily accompany anoxia are prevented by the inhalation of small concentrations of carbon dioxide together with the oxygen-nitrogen gas mixture, it is found that blood pressure rise and respiration are markedly increased over and above the values obtained in pure anoxia. Moreover, it is found that the addition of carbon dioxide makes anoxia a more powerful stimulant of the sympathetico-adrenal system than is anoxia per se. These observations seem to indicate that a moderate

retention of carbon dioxide in anoxia elicits more powerful adjustment reactions to anoxia than does oxygen lack alone. This holds true not only for those reactions which improve the transport of oxygen to the tissues, but also for those processes which reduce the oxygen demands of the tissues by reduction of the temperature of the body. The better oxygenation of the tissues in asphyxia produced by the inhalation of oxygen-nitrogen mixtures containing some excessive carbon dioxide is illustrated by the fact that various functions of the brain are better preserved under these conditions than in similar experiments involving anoxia alone.

4. The fundamental observation that the vasomotor center is excited by anoxia while other cerebrospinal functions, except those involving the respiratory apparatus, are depressed, seems to be due to the fact that the sensitivity of autonomic centers to anoxia is considerably less than that of somatic centers. This may cause autonomic centers to react with signs of marked increased activity while somatic centers are depressed. This interpretation is supported by experiments in which various autonomic and somatic functions are studied under the influence of anoxia.

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HEMOLYTIC STREPTOCOCCAL PNEUMONIA AND EMPYEMA; A STUDY OF 55 CASES WITH SPECIAL REFERENCE TO TREATMENT *

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IT is now well established that at least 85 to 90 per cent of all cases of pneumonia are due to pneumococcal infections and, of these, at least 80 per cent are caused by a relatively small number of specific types (I, II, III, V, VII, VIII, and XIV). Other microörganisms, such as *Streptococcus hemolyticus, Staphylococcus aureus, Bacillus Friedlander,* are usually responsible for the remaining cases. The hemolytic streptococcus is the cause of between 3 and 5 per cent of all cases of pneumonia although its frequency varies from time to time, depending somewhat upon the predisposing factors and the existence of epidemics of respiratory infections which create favorable conditions for the invasion of the organisms.

As a part of an investigation of hemolytic streptococcal infections, 55 cases of infection of the lungs and pleura were studied. In particular, we were concerned with the determination of the specific types of hemolytic streptococcus causing these infections and the effect of the newer chemotherapeutic agents in treatment.

ANALYSIS OF CASES

Etiology and Predisposing Factors. Hemolytic streptococcal pneumonia occurs most often following epidemic influenza or measles; less often it is associated with pneumococcal infection or other inflammatory lesion of the lungs. In 10 of the 55 cases which were studied, the infection of the lungs, insofar as could be ascertained, was primary. That is to say, it occurred without any preceding illness. In 13, the pneumonia was preceded by an infection of the upper respiratory tract and, in an additional 10, it was associated with pneumococcal infection. Other predisposing factors are listed in table 1.

Of considerable importance was the association of hemolytic streptococcal pneumonia with chronic processes in the lung, such as asthma, bronchiectasis, and chronic cystic disease of the lung. In these chronic infections, the acute pneumonia was caused by the hemolytic streptococcal infection and the underlying disease could be established only after the acute

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From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston.

TABLE I

	Total Number of Cases	Empyema
1. Primary pneumonia	10	4
2. Upper respiratory infections, tonsillitis, scarlet fever	13	2
3. Associated pneumococcus infections	10	4
4. Chronic pulmonary infection	13	
Asthma	3	
Bronchiectasis	2	
Bronchitis	2	
Cystic disease	1	
Tuberculosis	1	1
Abscess	3	1
Pulmonary infarct	1	1
5. Bacteremia	1	1
6. Miscellaneous		
Associated heart disease	4	
Post-operative pneumonia	2	
Hemothorax		1
Mediastinitis		1

process had subsided. The presence of a chronic process in the lungs was also suggested from the history of the preceding illness in many cases.

Age. The cases were fairly evenly distributed throughout the second to the sixth decades, and only single cases were included in the first and eighth decades. Ten of the 16 cases of empyema were observed under 40 years of age. There was only one death under 30 years of age, whereas 6 of the 10 deaths occurred in patients over 40 years of age. The incidence of empyema was most striking under 30 years of age, although there were only three deaths in patients with empyema; one occurred under the age of one year and the other occurred in a man with a complicating heart disease (table 2).

TABLE II

Age Distribution With and Without Empyema

Age Groups	Total Cases	Empyema	Deaths
0–9	1	1[1]	1
10–19	13	7	0
20–29	8	2	0
30–39	7	0	1
40–49	9	4[2]	2
50–59	10	0	1
60–69	6	1	5
70+	1	1	0
	55	16	10

White Blood Cell Counts. In those patients with pneumonia uncomplicated by empyema, the total white blood cell count varied between 7,000 and 59,000 per cu.mm. The average was between 10,000 and 30,000 per cu. mm. In the presence of empyema, the leukocyte count was usually higher since over half of the cases showed 40,000 or more cells. In the fatal

cases, the total leukocyte count was under 20,000 in all but one. In brief, it would appear that patients with empyema due to hemolytic streptococci are likely to show high leukocytosis (12,000 to 78,000). This is in striking contrast to the case reports [1] of hemolytic streptococcal pneumonia following epidemic influenza, in which the leukocyte count may fail to increase when pneumonia develops.

Bacteremia. The presence of hemolytic streptococci in the blood is always of serious prognostic significance although it is relatively infrequent in patients with hemolytic streptococcal pneumonia. Seven of the 55 patients showed bacteremia (12 per cent). Four of them died and the other three recovered, giving a fatality rate in the bacteremic cases of 57 per cent. This is in marked contrast to the fatality rate in the non-bacteremic cases, which was only 9 per cent. Of the bacteremic cases, only two were under 50 years of age. This suggests, of course, that the age of the patient influences the incidence of bacteremia in hemolytic streptococcal pneumonia just as it does in pneumococcal pneumonia.[2] With the exception of one patient who had empyema, which was secondary to a metastatic pneumonia, none of the patients with empyema showed bacteremia.

Specific Types in Pneumonia and Empyema. Through the courtesy of the Lederle Laboratories, Inc., who supplied us with serum, we were able to study the various specific types of hemolytic streptococci which were isolated. With the sera which were available, we were able to identify 32 of the 55 strains which were isolated from either the sputum, the blood, or the empyema fluid. They were distributed as follows.

TABLE III

Types of Hemolytic Streptococci Isolated in 55 Cases of Pneumonia and Empyema

Types	Pneumonia	Empyema
I	3	—
II	4	—
IV	1	—
XII	3	2
XIII	5	2
XV–XVII	15	5
XXVII	1	
Unidentified	23	7
Total	55	16

ANALYSIS OF VARIOUS GROUPS

Hemolytic Streptococcal Pneumonia Without Any Preceding Illness. In 10 cases, the pneumonia was not preceded by any illness and was considered to be a primary pneumonia. There was nothing distinctive about these cases. The onset was frequently abrupt with the symptoms of an acute infection and the local signs of pneumonia which were frequently diffuse in character and only rarely associated with frank signs of lobar con-

solidation. The etiologic diagnosis was made by examination of the sputum. In uncomplicated cases, the disease varied in duration from 7 to 21 days. There were two deaths in this group. One occurred in a woman 60 years of age who had bacteremia and a rapidly progressing illness of only seven days' duration. The other was a woman 66 years of age who had a prolonged illness of 49 days' duration and bacteremia on one occasion.

Hemolytic Streptococcal Pneumonia Preceded by an Acute Respiratory Infection or a Hemolytic Streptococcal Infection of the Throat. In a second group of 13 cases, the pneumonia was preceded by an acute upper respiratory infection, such as a common cold, pharyngitis, or tonsillitis. In these, the onset of the pneumonia was always associated with an increase in the severity of the symptoms. Examples of cases of pneumonia following tonsillitis and scarlet fever are illustrated in figures 1 and 2.

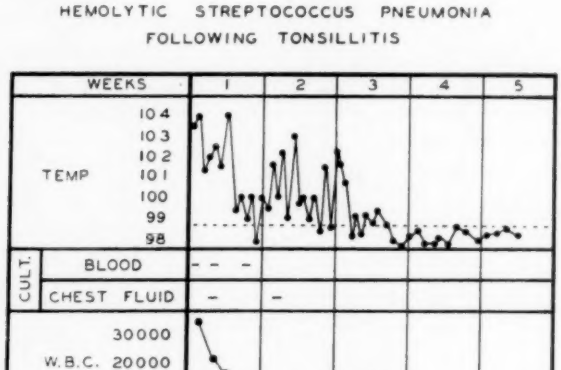

FIG. 1.

Hemolytic Streptococcal Pneumonia and Sterile Pleural Effusion Following Acute Tonsillitis.

Case 1. A young girl, 14 years of age, developed all the symptoms and signs of acute follicular tonsillitis one week before admission to the hospital. Three days after the onset of her illness she developed an acute pain in the right side of the chest, cough, and the expectoration of mucopurulent sputum. On examination, it was found that she had fever, leukocytosis, and the signs of a bronchopneumonia over the lower lobe of the right lung. The sputum contained numerous Type XIII hemolytic streptococci and the blood culture was negative.

Course of Illness. The course of the illness is charted in figure 1. The fever continued for 17 days. The blood cultures were always negative. On the third day of observation there were distinctive signs of a pleural effusion on the right side, and

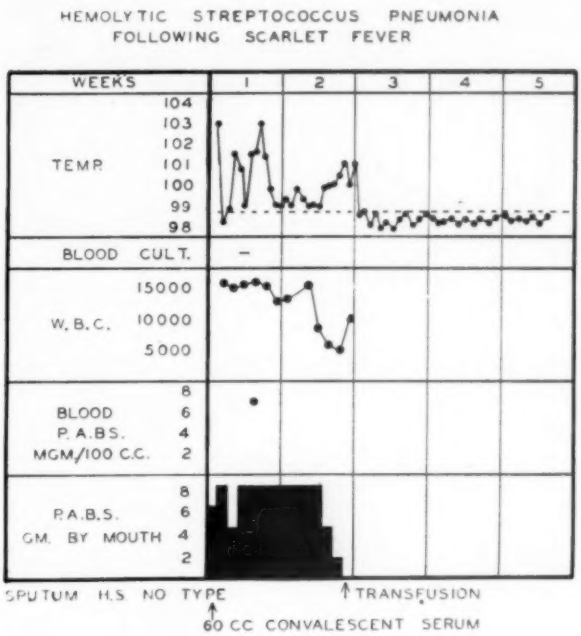

FIG. 2. P. A. B. S. Sulfanilamide.

200 cubic centimeters of hemorrhagic fluid were withdrawn from the chest. No organisms were found on either smear or culture. The chest was aspirated again on the eighth day of illness but the fluid continued to be sterile. After this aspiration the fluid disappeared. At first, there was high leukocytosis which decreased as the disease progressed. From the second to the eleventh day of her illness she received large amounts of sulfanilamide; then the drug was discontinued temporarily on account of nausea and vomiting and some improvement in her general condition. However, when it was discontinued, there was an increase in the fever and signs of a spreading process in the left lung appeared. Sulfanilamide was started again and continued for another six days, at which time the temperature had returned to normal.

Comment. There were several features of this case worthy of comment: first, the sterile effusion which disappeared after two aspirations without signs of purulent infection and, second, the exacerbation of fever and the spread of the process following the discontinuance of sulfanilamide. Both of these features stress the importance of continuing chemotherapy until all signs of active infection have disappeared.

Case 2. A woman, 34 years of age, developed scarlet fever at the end of a full term pregnancy. Two days after the onset of the sore throat she delivered a normal baby but continued to have fever varying from 100 to 104°. When she was seen in the hospital her temperature was 103°, the tonsils and throat showed the signs of an acute infection, and there was an eruption of the skin characteristic of scarlet fever. Two days later there were signs of pneumonia over the right lower lobe. The sputum contained many hemolytic streptococci and the blood culture was negative.

Course of Illness. This is shown in figure 2. On admission the patient was given 60 c.c. of anti-scarlatinal convalescent serum. This was followed by a prompt dis-

appearance of the rash and a striking decrease in the temperature. However, with the appearance of the signs of pneumonia, the temperature once again became elevated and continued for 14 days. Sulfanilamide was started on the day of admission and continued for 13 days, when it was stopped on account of a progressive anemia and a declining leukocyte count. She was given a blood transfusion on the fourteenth day and recovered completely.

Comment. This patient received convalescent serum for the toxic features of her infection and sulfanilamide for the local infection in the throat and lungs. It was also necessary to give her a blood transfusion for the progressive anemia. Her recovery was complete. This case serves to illustrate the importance of using antitoxic serum as well as chemotherapy in patients with scarlet fever complicated by a septic infection such as pneumonia.

In this group of cases there were no deaths. This was probably due to the fact that the patients were all under 40 years of age, none of them had bacteremia, and they were all treated promptly with sulfanilamide.

Hemolytic Streptococcal Pneumonia Following Bacteremia. In a previous study[3] of 246 cases of hemolytic streptococcal bacteremia it was found that metastatic pneumonia occurred in 7.3 per cent of cases. Usually the fatality rate in these cases is exceedingly high unless active and energetic treatment is employed. Recovery may follow, however, when sulfanilamide is given in large amounts. The following case is an example.

Case 3. A young boy, 13 years of age, was admitted to the hospital complaining of pain in the right foot and ankle and high fever. He had been well until three days before admission when he became acutely ill with fever and great prostration. This was soon followed by pain, swelling, and redness in the right foot and ankle. Examination showed high fever, râles over the right lung posteriorly, and the signs of infection of the right ankle joint. The blood culture was positive for Type XIII hemolytic streptococci and there was leukocytosis.

Course of Illness. The fever and leukocytosis persisted for five weeks, and for 10 days there was bacteremia (figure 3). The signs of pneumonia increased over the right lung until signs were elicited over all three lobes. In the fourth week there were signs of a small empyema in the right pleural cavity and hemolytic streptococci were isolated from the pleural fluid on two occasions. The signs of an acute fibrinous pericarditis were present for three days during the fourth week of the illness. The patient was treated with large doses of sulfanilamide and multiple blood transfusions. The sulfanilamide was continued for 16 days until the blood was sterilized, and it was then discontinued temporarily because of the anemia which progressed in spite of the multiple blood transfusions. It was started for a second time when the empyema was discovered. After an illness of 10 weeks this young boy recovered completely.

Comment. The striking features of this case were: (1) the hemolytic streptococcal bacteremia without an obvious focus of entry; (2) the metastatic lesions in the ankle joint, lungs, pleura, and pericardium; (3) the complete recovery following sulfanilamide and multiple blood transfusions without the surgical drainage of the empyema.

One should note in this case, and it is true in most cases of hemolytic streptococcal sepsis, that the blood stream is not cleared promptly following

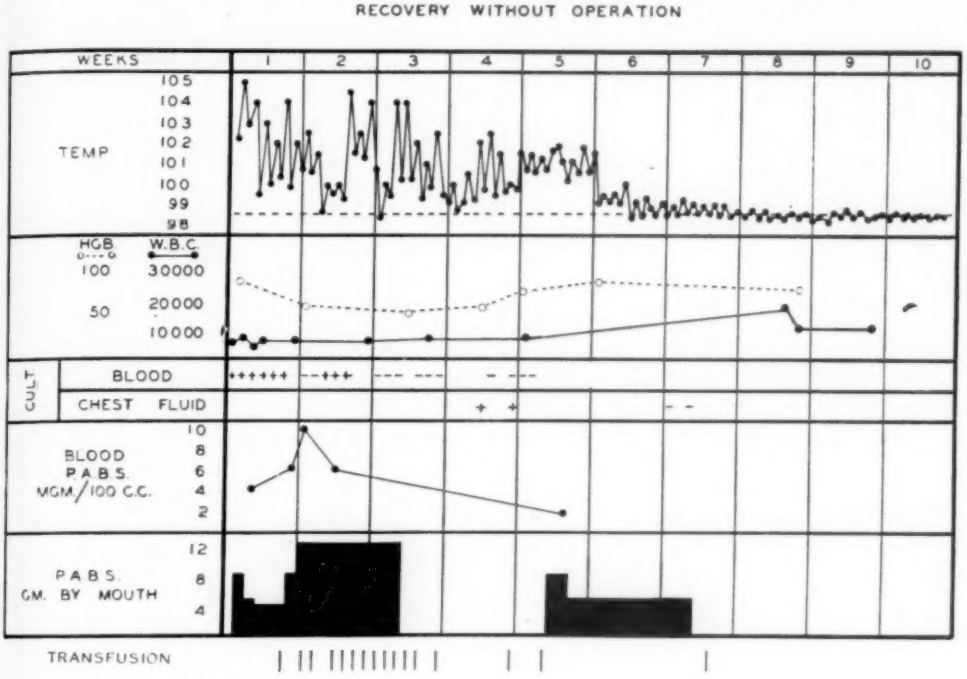

FIG. 3. Chart illustrating the course of disease and treatment of hemolytic streptococcal bacteremia with pneumonia and empyema with sulfanilamide and multiple blood transfusions.

the use of sulfanilamide. Moreover, it was necessary to use multiple blood transfusions in order to prevent a rapidly progressive anemia. When these procedures are followed, recovery will follow in many cases. One should remember, however, that it is rare indeed to observe any dramatic or sudden change in the patient's condition following the use of sulfanilamide. The fact that they recover is impressive. Long-continued treatment is necessary for the best results.

Hemolytic Streptococcal Pneumonia Associated with Pneumococcal Infection. In 10 cases, the hemolytic streptococcus was associated with the pneumococcus as a cause of the pneumonia. The importance of mixed infections in the causation of pneumonia has been studied and reviewed recently by Finland [4] who showed that most of the mixed infections were due to the pneumococcus and the hemolytic streptococcus. Cases of mixed infections have also been reported by Parsons and Myers [5] and Solomon and Curphey.[6] The types of pneumococci which were isolated along with the hemolytic streptococcus in our cases were Types I, III, VI, VIII, IX, XIX, and XI. In some cases, the hemolytic streptococcal infection was demonstrated when the pneumococcal infection was active. In others, the pneumococcal pneumonia was complicated by a hemolytic streptococcal abscess

of the lung, an empyema, or mediastinitis. In several instances, a relapse of the pneumonia or a reinfection of the lung was caused by the hemolytic streptococcus.

These cases of mixed infection comprise an important group since their course is often atypical, the complications are numerous, and the results of treatment may be difficult to interpret. Finland [4] has shown that at least 6 per cent of all patients with pneumococcal pneumonia have evidence of a mixed infection of the lungs. He divided his cases into three groups: (1) those in which only one of the multiple organisms isolated from the sputum was responsible for the pulmonary infection; (2) those in which more than one organism had invaded the lung simultaneously, either at the same or different sites; and (3) those in which invasion by one organism followed the other. In these cases, with a relapse of infection, the same or different sites of the lung are involved. The cases which were reviewed by Solomon and Curphey [6] probably belong in group 3, although it was not always possible to demonstrate a new focus in the lungs at the time of the hemolytic streptococcal bacteremia. In some, the bacteremia occurred following the recovery from the pneumococcal infection, and in others there were signs of delayed resolution of empyema. In any event, the sputum should be studied in all cases of pneumonia for evidence of a mixed infection and the blood should be cultured repeatedly in patients who have a protracted course and who are not responding to treatment.

Hemolytic Streptococcal Pneumonia in Patients with Chronic Pulmonary Disease. A common feature of chronic pulmonary disease is acute attacks of pneumonia. In 13 of the cases of hemolytic streptococcal infection, there was some chronic pulmonary disease preceding the attack of acute pneumonia. These cases included asthma, bronchiectasis, bronchitis, abscess of the lung, tuberculosis, and cystic disease of the lung. The diagnosis of the chronic disease of the lung was made from the history or from the condition of the lungs following recession of the acute process. There was one death in this group occurring in a 36 year old patient with bronchial asthma. All of the other patients recovered from their acute infection.

Usually, the course of events in these cases is as follows. A patient with a chronic pulmonary infection becomes acutely ill with high fever, prostration, and the signs of a diffuse pulmonary infection. The sputum is abundant and contains numerous hemolytic streptococci. After a period lasting from two to six weeks, the acute process gradually subsides, leaving the chronic process which may be quiescent or latent, or it may remain active. Not infrequently the process is repeated over a period of months. Each time hemolytic streptococci or other organisms may be isolated from the sputum.

Hemolytic Streptococcal Pneumonia in Miscellaneous Conditions. This group of six patients (table 1) illustrates the importance of chronic disease such as cardiac insufficiency in influencing the outcome of hemolytic strep-

tococcal pneumonia, since all four of the patients with heart disease and pneumonia died. Two had bacteremia and they were all 50 years of age or older. The other two cases in the group occurred following abdominal operations.

Analysis of Fatal Cases

There were 10 deaths in the 55 cases, or a gross fatality rate of 18.1 per cent. It was highest (57 per cent) in bacteremic cases and lowest in the non-bacteremic cases. Five of the patients had bacteremia and six were over 50 years of age. These points serve to stress the importance of age and bacteremia in influencing the outcome. One patient was only 10 months of age and had a complicating empyema.

The specific types of hemolytic streptococci which were present included Types I, II, XII, (XV–XVII). Death occurred within seven days after the onset of infection in four and between 21 and 48 days in the remaining five cases.

Factors which contributed to an unfavorable outcome were the presence of heart disease, asthma, and arteriosclerosis. There were three deaths among the patients with empyema, one in an infant 10 months of age, one in a patient with empyema following traumatic hemothorax, and a third in a patient with empyema associated with an infected infarct in heart disease.

The following is a list of the fatal cases.

1. Rapidly progressing infection with bacteremia in a woman 60 years of age.
2. Pneumonia in 5 patients with heart failure, aged 50, 60, 66, 60, and 34 years, respectively.
3. Multiple lobes involved in a woman 36 years of age with bronchial asthma.
4. Three patients with empyema.

From the study of this small group of cases, it would appear that age, bacteremia, complications, and associated debilitating diseases are important in prognosis.

Empyema

Sixteen of the 55 patients had empyema, and death occurred in three. In 11, the empyema was associated with pneumonia. In seven, the pneumonia was due to the hemolytic streptococcus alone while, in four, there was an associated pneumococcal infection of the lung. The other causes for the empyema are listed in table 4.

The fatal cases occurred in a child 8½ months old, in the patient with the traumatic hemothorax, and in the man with the infected infarct of the lung.

Ten of the 16 cases occurred in patients under 30 years of age and, in general, it can be said that the incidence of empyema tends to follow the

TABLE IV

Empyema

(1) Streptococcal pneumonia	7
(2) Pneumococcal and streptococcal pneumonia	4
(3) Miscellaneous	
Tuberculosis of lung	1
Abscess of lung	1
Traumatic hemothorax	1
Mediastinitis following perforation of esophagus	1
Infected infarct	1
	16

frequency curve for hemolytic streptococcal pneumonia. It was most common under 20 years of age and over 40 years. Among the patients with hemolytic streptococcal infection of the lungs 13 (or 24 per cent) of the 53 developed empyema. It was most frequent in patients who had pneumonia without any preceding chronic pulmonary infection. In this group of 34 cases, there were 11 with empyema or 32 per cent.

The empyema usually occurred during the active stage of the pneumonia and, with the exception of the patients who had only a small amount of purulent fluid in the pleural cavity, the course was protracted and lasted from 6 to 14 weeks or longer.

Once the signs of empyema developed, the features of a septic infection were conspicuous; that is, irregular fever, high leukocytosis, a progressive anemia, and loss of weight. In those who had a thoracotomy with drainage of large amounts of fluid from the chest, malnutrition and hypoproteinemia were occasionally seen.

Treatment of Empyema. For purposes of discussion, the cases are divided into two groups: (1) those recovering without thoracotomy and (2) those recovering following operation. All of the patients received either sulfanilamide or sulfapyridine.

Patients Recovering Without Thoracotomy. There were four patients in this group. They were all treated with chemotherapy and aspiration of the chest. In two, the amount of purulent fluid was small and did not exceed 15 c.c. with each aspiration. In the remaining two, the amount of fluid aspirated each day varied between 150 and 300 c.c.

The following case illustrated the course of events in a patient recovering without thoracotomy.

Case 4. A young man suddenly became ill with the symptoms and signs of pneumonia involving the left lower lobe of the lung. There was high fever and leukocytosis. The blood culture was negative. On the third day of his illness signs of fluid appeared over the left lower lobe and aspiration of the pleural cavity disclosed 500 c.c. of thin, serous exudate containing Type XV/XVII hemolytic streptococci. The chest was tapped daily for 5 days and, in all, 1050 c.c. of fluid were removed. Organisms were isolated from the fluid on the first four days but on the fifth day the fluid was sterile. He recovered completely and was discharged from the hospital 6 weeks after admission. From the first day of his illness and for a period of 11 days, he received 4 grams of sulfapyridine a day, a total of 44 grams. Three days after the pleural fluid became sterile, the drug was discontinued.

Comment. This case is an example of recovery following repeated aspirations of the pleural cavity and chemotherapy. The interesting feature is that the fluid was sterilized within five days of the beginning of treatment and while the pneumonia was still active.

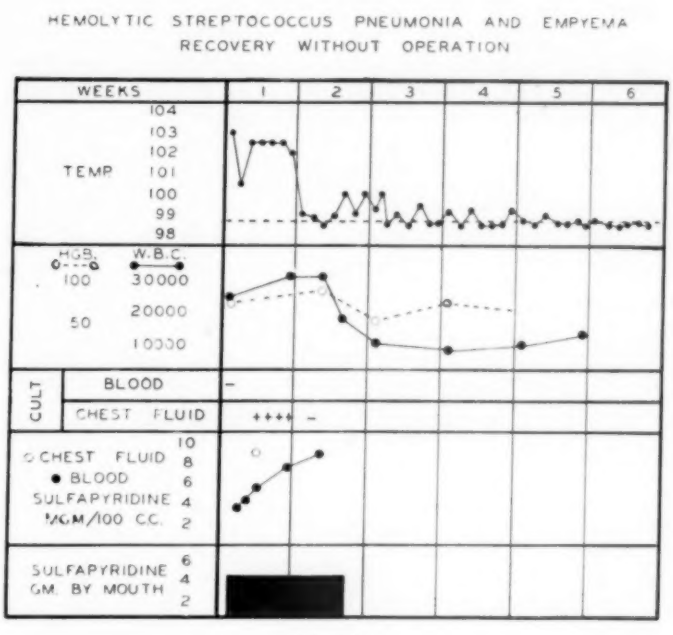

FIG. 4.

The following case illustrates the recovery of pneumonia and empyema following aspiration of the chest and chemotherapy. It also illustrates the fact that acute rheumatic fever will occur following hemolytic streptococcal infection in spite of energetic and active chemotherapy.

Case 5. A young boy, 15 years of age, had been ill with the symptoms and signs of pneumonia for five days before admission. When he was seen on the sixth day of his illness he had fever, leukocytosis, and the signs of pneumonia over the left lower lobe. The sputum contained many hemolytic streptococci which could not be typed with the sera that were available. The blood culture was negative. Two days after admission there were signs of fluid in the left pleural cavity and, when a needle was inserted into the chest, 7 c.c. of fluid containing many hemolytic streptococci were withdrawn. Sulfanilamide was started and continued in large amounts for five weeks.

Cases of Empyema Recovering Following Thoracotomy. There were nine patients with empyema who recovered following chemotherapy and thoracotomy. These cases were of special interest since all of them received sulfanilamide prior to operation in an attempt to sterilize the empyema. A number of facts emerged from the study of these cases which aid greatly in the management of cases of empyema when chemotherapy is used. These points can be illustrated by several cases.

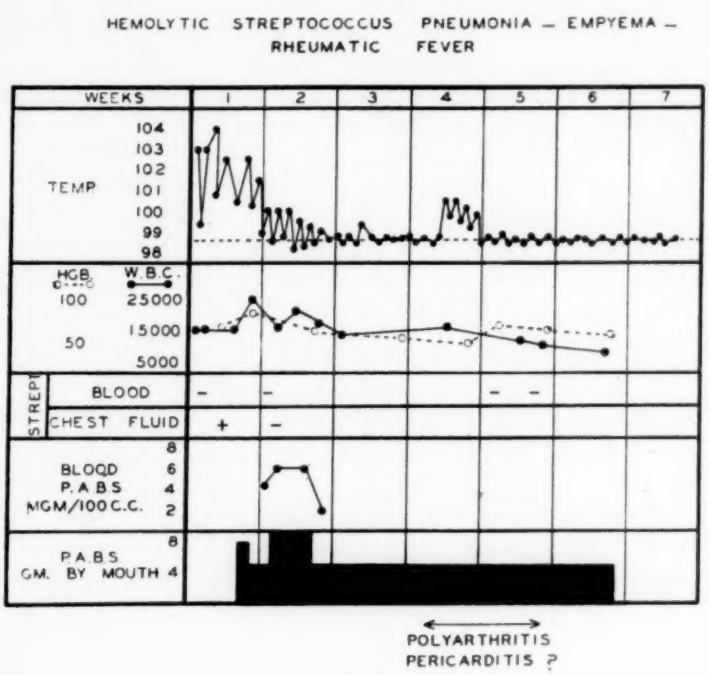

FIG. 5.

Case 6. A girl, aged 15 years, with hemolytic streptococcal pneumonia and empyema recovers temporarily following aspiration of the chest and chemotherapy. Complete recovery follows thoracotomy.

A young girl, 15 years of age, was ill for six days with fever and sore throat before admission to the hospital. She had fever, leukocytosis, the signs of pneumonia over the lower lobe of the right lung, and Type XV/XVII hemolytic streptococci in the sputum. The blood culture was negative. On the seventh day after admission there were signs of fluid in the chest in spite of the fact that the temperature was lower. The chest was tapped on the eighth day of the illness and 2000 c.c. of thin, serous fluid containing hemolytic streptococci were removed. This was repeated on five occasions during a two-week period, and a total of 3150 c.c. of fluid were aspirated from the chest. During this period she was given large amounts of sulfanilamide and four blood transfusions. The temperature remained normal for three weeks and she was discharged home for two weeks but she again returned to the hospital with high fever and the physical signs of a recurrence of the empyema. The blood cultures were negative. The chest was again tapped and a small amount of infected fluid removed. Sulfanilamide was started once again but, in spite of a temporary decrease in temperature, the pleural fluid continued to be infected and reaccumulated. Recovery followed thoracotomy. The course of the illness is shown in figure 6.

Comment. In this case there was a temporary recovery from an empyema following multiple aspiration of the chest and chemotherapy. Indeed, the results were so striking that the patient was allowed to return to her home. After a period of five weeks, there was a recurrence of symptoms and signs of empyema and recovery occurred only after free drainage of fluid

was obtained. It is well, therefore, to follow all patients for a considerable period of time following chemotherapy and aspiration of the chest since there may be a recurrence of infection in spite of a temporary disappearance of all signs of active infection.

The following case illustrates how chronic the course of a hemolytic streptococcal empyema may be in spite of chemotherapy, drainage of the empyema cavity, and thoracotomy.

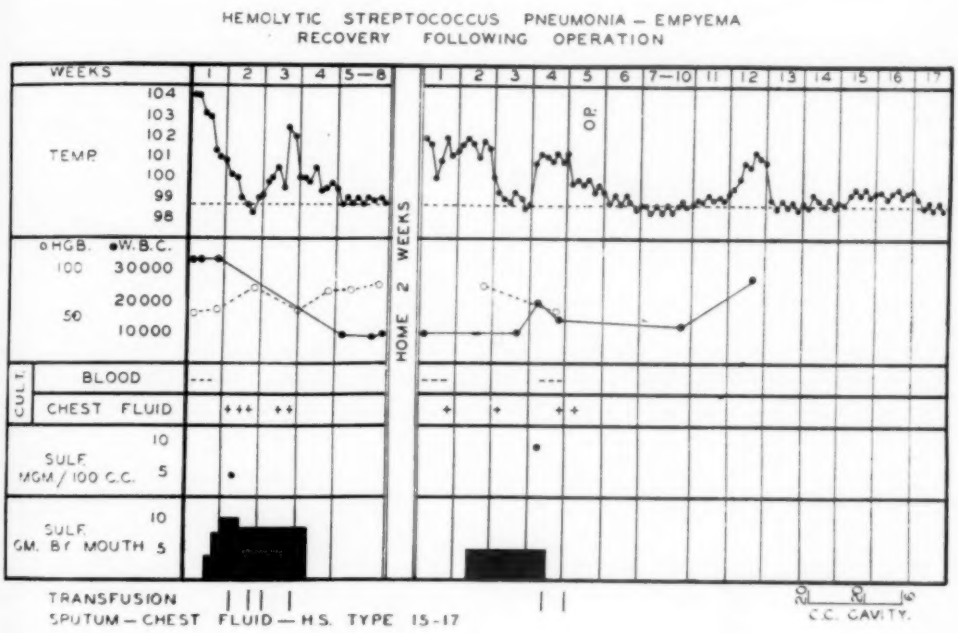

FIG. 6.

Case 7. A boy, 15 years of age, was admitted to the hospital during the first week of an acute illness. At the time of admission he was found to have the signs of pneumonia and empyema of the left lung and pleura, respectively. The sputum contained Type XII hemolytic streptococci. The blood cultures were negative but the fluid aspirated from the left pleural cavity contained many Type XII hemolytic streptococci. He was acutely ill and, during the first seven days of observation, 3000 c.c. of thin, serous fluid were aspirated from the left chest. On the eighth day a closed thoracotomy was done but, since there was very little improvement and inadequate drainage, a rib resection was done on the fourteenth day of his illness. He was given multiple blood transfusions for a progressive anemia and the pleural cavity was irrigated with sulfanilamide in a concentration of 20 mg. per 100 c.c. There was gradual but progressive improvement for nine weeks when he was discharged from the hospital. He remained at home for eight weeks and then returned on account of fever and pain in his chest. It was found that he had a recurrence of a small empyema at the site of the original infection. The cavity was opened, chemotherapy was started again, and he recovered promptly. These episodes were repeated on three different occasions until 10 months after the onset of his illness when it was found that he had a sinus leading from the chest wall into a small cavity and there was a *Staphylococcus*

aureus infection. Following excision of the sinus and establishment of free drainage he finally recovered completely. The clinical course is illustrated in figure 7.

Comment. In spite of large amounts of sulfanilamide and multiple aspirations of the chest, it was not possible to influence the course of this boy's illness in a favorable sense until a thoracotomy was done. Even then, he had several recurrences of the local infection. This case, then, is an example of the chronic character of some cases of hemolytic streptococcal empyema, and it also serves to emphasize the fact that all available forms of treatment must be used in order to effect a cure.

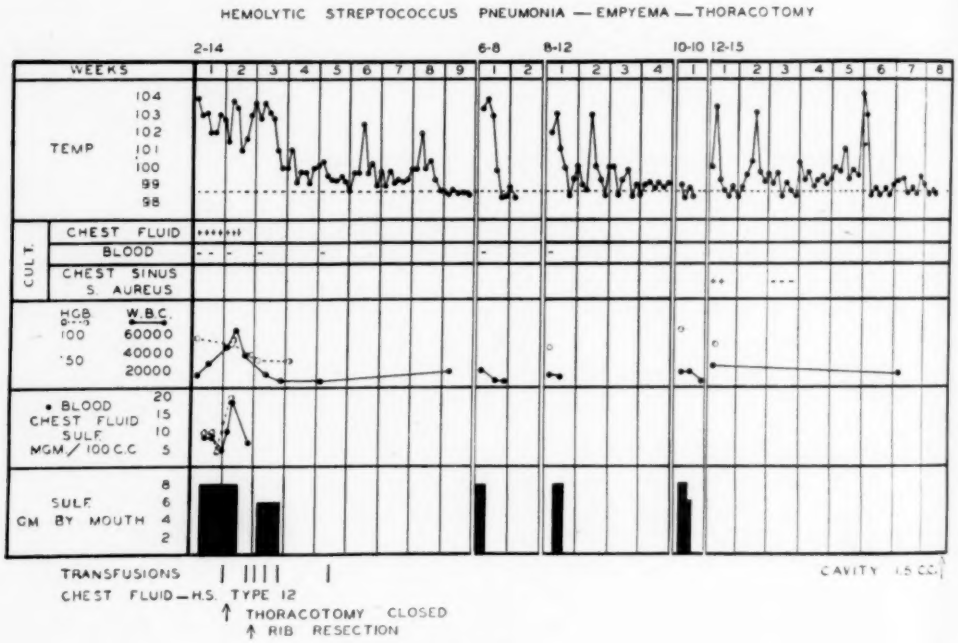

FIG. 7.

The next case demonstrates that the fluid in the pleural cavity may be sterilized temporarily following repeated aspirations of the chest and chemotherapy but, once it is discontinued, the infection may recur so that surgical operation is necessary.

Case 8. A boy, 13 years of age, became ill with the symptoms and signs of pneumonia. Within two days after admission to the hospital there were signs of a left-sided pleural effusion. There were high fever, leukocytosis, and negative blood cultures. The sputum contained many Type XII hemolytic streptococci. The pleural fluid was thin and serous and contained many Type XII hemolytic streptococci. During the first two weeks of observation the pleural cavity was tapped three times and 1630 c.c. of infected fluid were withdrawn. Sulfanilamide was given by mouth for 10 days and was discontinued on account of an anemia. Three blood transfusions were given, as indicated in figure 8, for the anemia and to replace plasma protein

which was being lost from the multiple aspirations of the chest. The patient had developed moderate edema of the ankles and the plasma proteins were 6.1 grams per 100 c.c.

During the third week, the temperature ranged between 99 and 99.5° and 250 c.c. of fluid aspirated from the chest were sterile. This was somewhat misleading inasmuch as the patient continued to have low-grade fever. Finally, during the sixth week, 55 c.c. of fluid were again withdrawn and proved to be infected. A thoracotomy was performed and free drainage was established. He recovered gradually and, with the exception of an intercurrent respiratory infection during the eleventh week, he recovered completely. The course of his illness has been charted in figure 8.

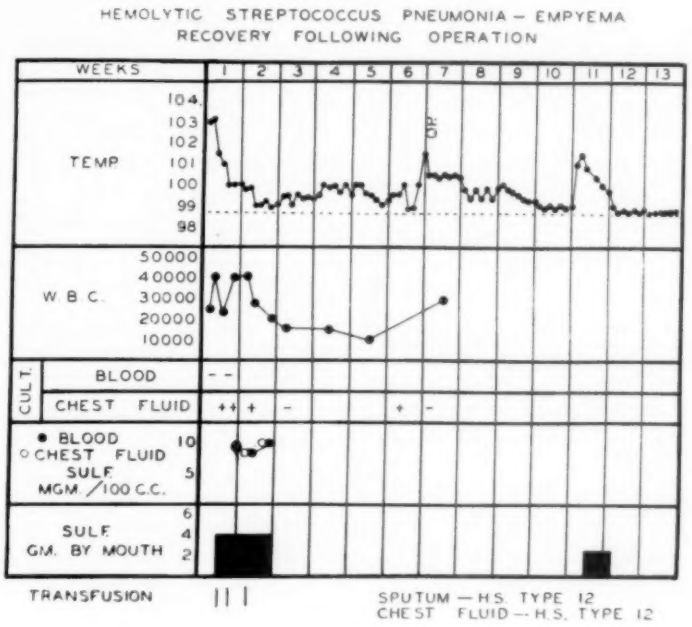

FIG. 8.

Comment. In this case, the pleural fluid was sterilized temporarily following sulfanilamide and aspiration of the pleural cavity, but complete recovery followed the establishment of free drainage of the empyema cavity. One should not be deceived by the temporary sterilization of the fluid in these cases since, on a number of occasions, we have observed that this temporary improvement has been followed by a reinfection of the fluid and recovery only follows surgical treatment.

COMMENT

From our own studies and those of others, it seems plain that the hemolytic streptococcus is a frequent secondary invader in the lung. It infects the lung following measles, epidemic influenza, the common cold, sore throat, or erysipelas. Occasionally it acts as a secondary invader in pneumococcal

pneumonia, and not infrequently metastatic pneumonia due to this organism occurs in patients with streptococcal bacteremia. Bronchiectatic abscess cavities as well as cysts of the lung are infected frequently with streptococci, and sterile pleural effusions following lung tumors, or pulmonary infarcts may become infected.

Characteristically, the hemolytic streptococcus produces an interstitial or confluent bronchopneumonia. It is followed by empyema in a high percentage (20 per cent) of cases, and suppurative lesions of the lungs (bronchiectasis and lung abscess) are not uncommon. Mediastinitis, pericarditis, and suppuration of the subcostal lymph nodes are not infrequent lesions in the fatal cases. Bacteremia occurs in only about 10 to 15 per cent of cases and, commonly, as a late event in the course of the disease.

The fatality rate has been reported as varying between 30 and 60 per cent of cases. In our small group of 39 patients with pneumonia, it was only 17 per cent. Unfavorable factors in the course of the disease were age, bacteremia, and the presence of some chronic illness such as heart disease. The outcome will also depend upon the treatment employed and this will be commented upon presently.

The treatment of hemolytic streptococcal pneumonia prior to the widespread use of the sulfonamide group of drugs was largely supportive and symptomatic. Amoss and Craven [7] reported encouraging results from the use of anti-streptococcic serum in 1930, but this form of treatment has never received widespread use. The reason for this is the difficulty in typing hemolytic streptococci and in producing potent antibacterial as well as anti-toxic serum.

With the introduction of the sulfonamide drugs, a new group of therapeutic agents has been used with some success. It is difficult even now to make any remarks which can be considered to be final in respect to the efficiency of these drugs in the treatment of pneumonia due to this organism since there are so many variable factors in assessing the value of treatment in this disease. A few facts of significance have emerged; namely, sulfanilamide does not produce any dramatic change in the course of hemolytic streptococcal pneumonia, and it does not seem to reduce the incidence of empyema. It is perhaps significant that there was only one death in 28 patients between the ages of 10 and 40 years, and in this group there were nine cases of empyema. Moreover, in the 16 patients with empyema, there were only three deaths and, in all, there were other unfavorable factors which influenced the outcome of the disease, such as age (one patient was less than one year of age), heart disease, and traumatic hemothorax. It would appear, therefore, that sulfanilamide will influence the outcome of hemolytic streptococcal pneumonia and empyema in that it will reduce the fatality rate.

In a recent study of 78 cases of hemolytic streptococcal empyema by Nowak,[8] the fatality rate in patients who did not receive sulfanilamide was

48 per cent, whereas in those who received it, the fatality rate was 29 per cent. Leahy [9] of Buffalo has also reported his observations in seven cases of hemolytic streptococcal empyema treated with sulfanilamide, aspiration of the chest, or open thoracotomy with only one death. With the exception of one patient, who was 20 years of age, all of his patients were under 10 years of age. Bacteremia was present in one. Sulfanilamide and multiple aspiration of the pleural cavity were used in four cases, all recovering. Sulfanilamide and rib resection were employed in one with recovery, and sulfanilamide and closed drainage in two resulted in one death. From these cases, it would appear that in some young patients multiple aspirations and sulfanilamide will be sufficient. In others, closed or open drainage will also be required. It is well to recall that surgeons of wide experience report recovery from hemolytic streptococcal empyema in about 10 to 15 per cent of cases following multiple aspirations.[10] It may be possible, especially when the pleural effusion is small, to increase the number of recoveries by this method without rib resection with the use of sulfanilamide or the other compounds.

Our experience so far, however, would indicate that even when sulfanilamide is used, open drainage of the pleural cavity will be required in most cases. One must not be misled or deceived by the temporary sterilization of the empyema cavity since we have observed recurrences of infection as long as three to five weeks after such an event. It is possible that treatment with sulfanilamide for a longer period of time after the fluid has been sterilized will increase the number of cures by this method. However, in our experience thus far, one must be guarded.

Aside from the use of chemotherapy and surgical treatment of empyema, other measures are of the greatest importance in the treatment of the patient. They all develop a progressive anemia which is accentuated by the sulfanilamide. For this reason, many of these patients are improved by using blood transfusions. Also, when large amounts of plasma protein are being removed from the chest, malnutrition and a plasma protein deficit may develop. This complication is treated most adequately by means of increasing the food intake and blood transfusions.

One may sum up the experience so far by saying that intensive chemotherapy reduces the fatality rate in hemolytic streptococcal pneumonia and empyema. It may also sterilize the pleural infection following multiple aspirations in some cases. In most instances, however, it neither shortens the course of the disease nor prevents the incidence of empyema. Chemotherapy, when used along with other forms of treatment, is of considerable value in the treatment of these infections.

Summary and Conclusions

1. Fifty-five cases of hemolytic streptococcal pneumonia and empyema have been studied and analyzed with respect to outcome and treatment, and

illustrative cases are presented. There were 39 cases of pneumonia alone and 16 cases of empyema. Fourteen of the 16 cases of empyema followed an infection of the lung.

2. The cases of pneumonia could be divided into three groups: (1) those which were primary; (2) those which followed a respiratory infection; and (3) those which were superimposed on a preëxisting chronic pulmonary infection.

3. The fatality rate in the 39 cases with pneumonia was 17 per cent. Unfavorable factors in influencing the outcome were age (i.e. over 50 years), bacteremia, and debilitating disease. The fatality rate in patients with empyema was 18 per cent, but it was striking that there was only one death from empyema between the ages of 10 and 40 years.

4. Bacteremia was present in 12 per cent of cases. It was more common in the patients over 50 years of age, and the fatality rate in bacteremic cases was 57 per cent, whereas in the non-bacteremic cases it was only 7 per cent.

5. The use of sulfanilamide or sulfapyridine did not reduce the incidence of empyema, and it was not possible to show that it shortened the course of the disease. There was suggestive evidence that the fatality rate in both the cases of pneumonia and empyema was reduced by using these drugs.

6. There were four cases of empyema which recovered following multiple aspirations of the chest and chemotherapy. The best results were obtained with a combination of chemotherapy and thoracotomy.

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CEREBRAL MANIFESTATIONS OF BACTERIAL ENDOCARDITIS *

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EMBOLIC lesions of the brain and cerebral vessels are as integral a part of bacterial endocarditis as are the embolic lesions of other structures, and the resulting neurological symptoms and signs merit equal importance with the café-au-lait coloring, clubbed fingers, enlarged spleen and conjunctival petechiae in the symptomatology of the syndrome.

Two cases recently seen on the wards of the Hospital Division of the Medical College of Virginia would have proved to be less puzzling diagnostic problems had this been realized. The first case was a colored male (Case 1) with a purulent meningitis, clubbed fingers and an enlarged heart without murmurs who was found to have a large vegetation on the aortic cusp at autopsy. The second case was admitted to the hospital, irrational and with a stiff neck (Case 2). Purulent spinal fluid containing blood was obtained on lumbar puncture. An aortic diastolic murmur was noted on examination, but the cardiac pathology was thought to be incidental until the spleen became palpable several days later and the fingers began to show early clubbing. With these two cases in mind, it was decided to survey the records of patients with bacterial endocarditis admitted over a period of several years and determine the frequency of occurrence and the types of cerebral lesions present in these.

Between June 1, 1932, and December 31, 1938, 35 patients with bacterial endocarditis were seen in the Hospital Division of the Medical College of Virginia. Seventeen (48.5 per cent) of these cases presented some type of cerebral sign or symptom and were selected for detailed study. Nine cases were admitted to the hospital primarily as neurological, neurosurgical or mental patients and made up 25 per cent of the total number of the 35 cases examined. Many of these patients were referred to the hospital for reasons quite foreign to the real issue, and some followed devious channels before being successfully diagnosed and arranged on the proper service. One was referred as a right frontal lobe tumor; another came from a distance of approximately 500 miles for the repair of an old skull fracture; a third came for psychiatric observation because he was accusing his fellow prisoners of poisoning his food and drink. Still another was rushed in by excited friends after the occurrence of a convulsive seizure, and a fifth patient descended on an unsuspecting house staff with a left hemiplegia and aphonia.

Meningitis, hemiplegia, subarachnoid hemorrhage and other neurological disturbances were noted from the very early descriptions of the disease.

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Osler [1] made several distinct references to such occurrences. More detailed studies, however, have for the most part been confined to the pathologic or purely neurological aspects. Kimmelstiel,[2] in 1927, made a thorough pathologic investigation of the brain lesions of subacute bacterial endocarditis in which he found inflammatory changes in the brain in 10 out of 13 cases. The outstanding, and most characteristic, change noted by this writer was a diffuse embolic encephalitis showing no predilection for any single portion of the brain substance. Microscopically the changes were characterized by glial proliferation, polymorphonuclear cell infiltrations with actual abscess formation in many instances, monocytic meningitis, ependymitis and inflammatory changes in the blood vessel walls. Less frequently did he note localized areas of ischemia and softening, degenerative changes in vascular structures and areas of hemorrhage into the brain substance. Diamond [3] in a detailed pathologic report noted similar changes and called especial attention to the formation of nodules of glial and mesodermal tissue, abscesses, degenerative areas, and inflammatory and degenerative changes in the blood vessel walls. De Jong [4] noted emboli and thrombi in cerebral vessels, subarachnoid and intraventricular hemorrhage, meningitis, brain abscess, and mycotic aneurysms. In his study of 68 cases, 17 presented clinical or pathologic evidence of central nervous system disease and six were admitted to the hospital on this account. Libman [5] noted the occurrence of cerebral emboli in 27 of 59 cases of subacute bacterial endocarditis and observed such symptoms as vertigo, headache, irritability, insomnia, delirium, stupor and coma in many of these cases. Winkelmann [6] in his description of the pathologic changes in 13 cases of bacterial endocarditis noted such conditions as meningitis, toxic endarteritis, organized emboli with degenerative brain changes, multiple abscesses and mycotic aneurysms. Lereboullet and Mouzon,[7] Smith and Brumfiel,[8] Tice,[9] Ullom,[10] Cabot,[11] Denman [12] and others [13-27] have reported cases of bacterial endocarditis with cerebral or other central nervous system manifestations.

Case Reports

Case 1. R. C., colored male, aged 42. Three and a half weeks before admission to the hospital the patient developed a severe cold and had to stop work. Shortly after this he developed a protracted cough which was productive of a thick, purulent sputum. Examined at this time by his family physician, he was told that he had some type of lung trouble and he was referred to the local tuberculosis sanatorium for further examination, and from there to St. Philip Hospital. The productive cough continued unchanged in character and, in addition, he developed a pain in his right chest which had been present for about three days before hospitalization. Inventory by symptoms and past history were non-contributory.

Physical examination: Temperature 101.6° F., pulse 90, respiration 22, blood pressure 110 mm. of mercury systolic and 70 diastolic. The patient was a well developed, well nourished colored male, lying quietly flat in bed, rational, alert, and cooperative. To general appearances he did not seem acutely ill. The head and neck were negative except for the presence of impacted wax in both auditory canals. There

was a prolongation of the expiratory phase over the right apex, but no definite evidence of pathologic change. The heart sounds were faint and distant, and the apex beat could not be visualized or palpated; nor could the left border be outlined by percussion. There were no murmurs. Abdominal examination was negative. A marked clubbing of the fingers and toes was present. All tendon reflexes were hypo-active; no pathological reflexes were noted.

Laboratory data: *urine,* amber, alkaline, specific gravity 1.032; albumin, sugar and acetone negative; sediment negative. *Blood:* 4,000,000 red blood cells; 78 per cent hemoglobin; 14,400 white blood cells; 88 per cent polymorphonuclear cells, 8 per cent lymphocytes, 4 per cent monocytes. Wassermann and Kline reactions were negative. *Blood culture:* 9–10–37, 9–11–37 and 9–13–37, pneumococcus type IV (group B). *Electrocardiogram:* 9–11–37, negative except for sinus tachycardia.

On 9–6–37 it was noted that the patient had a definite stiffness of the neck. A lumbar puncture was done, revealing a cloudy spinal fluid under 175 mm. of water pressure, containing 1,200 white blood cells, 96 per cent polymorphonuclear cells, 4 per cent lymphocytes; sugar 30 mg., globulin heavy trace, Wassermann and mastic negative. Smear and culture were negative. The patient was placed on sulfanilamide therapy both orally and intraspinally, but failed to respond to any appreciable degree. On 9–11–37 the following note was made: "The heart is enlarged to the left as indicated by the apex which is well to the left of the mid clavicular line; all second sounds are diminished in intensity, no murmurs are heard, the spleen is not palpated, the pulse is typically dicrotic and the fingers clubbed." Repeated lumbar punctures showed an elevated pressure with a white blood cell count which dropped from 1,200 on 9–6–37 to 145 on 9–12–37. The polymorphonuclear cell differential count was always in excess of 85 per cent. Repeated smears and cultures on this fluid were negative for any type of organism. The patient died on 9–19–37, 16 days after admission to the hospital.

Clinical diagnosis:

1. Septicemia, pneumococcic.
2. Meningitis, acute.
3. Chronic bronchitis.

Postmortem examination:

Autopsy diagnosis: Old healed endocarditis of aortic cusps and mitral valve; globular ulcerative endocarditis of aortic cusps and mitral valve; cardiac dilatation and hypertrophy; septic infarcts of kidney and spleen (spleen weight 200 gm.); bronchopneumonia, right lower lobe; caseation of hilar nodes, left.

Brain: The meninges covering the convexity of the brain were smooth, moist and glistening. At its basal portion, however, there was creamy pus in the subarachnoid space. Coronal sections revealed small hemorrhages 3 mm. in diameter at the border of the white and gray matter. The right occipital lobe showed multiple areas of softening which were well demarcated and rather large.

Histological examination: Various changes of inflammatory and degenerative nature were found throughout most of the brain sections. They were most marked in the pons, thalamus, posterior portion of the lenticular nucleus and in the occipital lobe. The following types were noted: 1. Small discrete nodules of glial proliferation intermixed with scattered polys and monocytes; in the center of one of these foci was a large mononuclear cell filled with diplococci. 2. Larger and more ill-defined foci of necrosis with large protoplasmic glial cells and hazy matrix with nuclear fragments and a few polymorphonuclear leukocytes. 3. Small abscesses. 4. Ill-defined foci of degeneration with crowded ganglion cells which undergo various types of degeneration and show evidence of neurophagia. 5. Perivascular infiltrations were found in various areas consisting of lymphocytes, monocytes and poly-

morphonuclear cells. 6. Rather marked meningitis was noticed which was of mixed nature, consisting of polymorphonuclear cells and monocytes. 7. A large area of softening in the occipital lobe which was characterized by loss of normal structure, accumulation of foam cells and crowding of numerous new formed capillaries with swollen endothelial cells. The greater part of the area of softening does not contain polymorphonuclear cell infiltration.

Final diagnosis:

1. Healed endocarditis of the aortic cusps and mitral valve.
2. Bacterial endocarditis, acute—pneumococcic.
3. Bronchopneumonia.
4. Meningo-encephalitis, embolic.

Case 2. L. M., colored female, aged 20. Until three weeks before admission to the hospital this patient was in excellent general health. At this time she first noticed a rather pronounced loss of appetite and a peculiar ringing sound in her ears which she described as sounding as if someone was "unwrapping packages." One week later she developed a severe generalized headache which was associated with a dizzy, unsteady sensation. These symptoms continued unchanged until the day before admission when she developed pain and a stinging sensation in both eyes, and shortly after this it was noticed that she could not see out of the right eye.

Physical examination: Temperature 103°, pulse 104, respiration 20, blood pressure 115 mm. of mercury systolic and 25 diastolic. The general appearance was that of an acutely ill, semistuporous person, lying flat in bed with eyes closed. She could be aroused to answer simple questions but then lapsed into a state of lethargy. The right conjunctiva showed a marked hyperemia with engorgement of the superficial vessels and swelling of both lids. The fundi were negative. The neck was stiff and attempts at anterior posterior flexion were accompanied by exquisite pain. No pathologic change was noted on examination of the chest and lungs. The apex beat was palpated in the fifth intercostal space almost in the anterior axillary line; no thrills were present. A systolic murmur was heard over the apex and a diastolic murmur over the aortic area. The pulmonic second sound was accentuated, and the pulse was of a collapsing type. The liver edge was palpated 2 cm. below the costal margin. On examining the extremities and reflexes, no contributory factors were noted.

Laboratory data: *Urine:* negative for blood and albumin. *Blood:* hemoglobin 60 per cent; white blood cells 25,300. *Serology:* Kline and Wassermann tests positive. *Blood culture:* positive for *Streptococcus hemolyticus. Spinal fluid:* white blood cells 403; polymorphonuclear cells 88 per cent; lymphocytes 12 per cent; red blood cells 1,650; culture positive for *Streptococcus hemolyticus* (third specimen).

On account of the stiff neck and febrile state, the case was thought at first to be one of meningitis, and a spinal puncture was done immediately. The fluid obtained was cloudy and under pressure. Sulfanilamide therapy was begun at once. There was no appreciable change, however, and on 10–30–37 an enlarged spleen and early clubbing of the fingers were noted, and the diagnosis of acute bacterial endocarditis with meningitis was substituted.

Clinical diagnosis:

1. Luetic heart disease.
2. Aortic regurgitation.
3. Acute bacterial endocarditis.
4. Meningitis, acute (*Streptococcus hemolyticus*).

Postmortem examination:

Autopsy diagnosis: Old healed endocarditis of the mitral valve with fresh superimposed globular vegetations; acute diffuse myocarditis and focal beginning abscesses;

large soft spleen (weight 320 grams); acute focal interstitial pneumonitis; embolic suppurative nephritis.

Brain: In gross showed slight injection of the vessels of the right cerebral hemisphere with a small subarachnoid hemorrhage over the base of the right temporal lobe. Coronal section revealed a rather large hemorrhage in the left collateral fissure measuring 4 by 1 by 1 cm. in diameter. There was a small cystic area in the left hemisphere just above the internal capsule.

Histological examination: 1. A large abscess was present in the white matter of the parietal lobe with complete liquefaction of the center containing masses of bacteria. 2. Foci of necrosis with very hazy matrix containing debris and some fibers surrounded by a wall of glial cells. These foci did not contain, or contained only a few, polymorphonuclear cells. 3. Many discrete nodules of glial proliferation which are rich in nuclei. 4. Irregularly distributed perivascular infiltration with round cells, monocytes and polymorphonuclear cells. 5. Meningitis was present in various areas, mononuclear in some instances and of a polymorphonuclear character in others. 6. Degenerative changes of ganglion cells were noticed in many areas. There was homogenization of the cytoplasm with disappearance of tigroid material and some neuronophagia.

Final diagnosis:

1. Healed endocarditis of the mitral valve and aortic cusps.
2. Acute bacterial endocarditis (*Streptococcus hemolyticus*).
3. Subarachnoid hemorrhage.
4. Meningo-encephalitis, embolic.

Case 3. J. H., colored female, aged 38. A colored female was admitted unconscious to the St. Philip Hospital on March 14, 1936. Twelve days before admission she had had a hard shaking chill while going about her usual household duties, and following this episode felt so weak that she had to go to bed. A few days after this abrupt onset, she developed a painful swelling in the left ankle and these symptoms continued unchanged until six hours before admission. At this time she had a generalized convulsion and she had remained unconscious thereafter.

Physical examination: Temperature 100.8°; pulse 90; blood pressure 118 mm. mercury systolic and 65 diastolic. An unconscious, middle-aged colored female, lying quietly in bed; respiration slow and blowing in character. The skin and mucous membranes were pale, and the face was covered with perspiration. A marked degree of nuchal rigidity was present. The chest and lungs showed no pathological change. A soft systolic murmur was noted over the cardiac apex. An indefinite mass was felt in the lower left abdominal quadrant. The left ankle was swollen, and the tissues "pitted" after digital pressure.

Laboratory data: *Urine:* heavy trace of albumin; white blood cells too many to count per high power field. *Serology:* Wassermann test negative. *Chemistry:* nonprotein nitrogen 138 mg. *Spinal fluid:* 150 white cells; 90 per cent polymorphonuclear cells, 10 per cent lymphocytes.

Immediately after admission a lumbar puncture was done, and a hazy fluid under 200 mm. of pressure was obtained. The patient died about five hours after entering the hospital.

Clinical diagnosis:

1. Meningitis, type not determined.

Postmortem examination:

Autopsy diagnosis: Healed endocarditis of the mitral valve; recurrent ulcerative endocarditis of the mitral valve; firm splenic tumor (weight 280 grams); interstitial

nephritis; purulent phlegmonous salpingitis; perirectal phlegmon with suppurative phlebitis.

Brain: There was a thick creamy purulent exudate in the subarachnoid space which was most profuse over the vertex. Sections of the brain showed no further pathological lesion.

Histological examination: (Section taken to demonstrate meningitis) purulent meningitis. There were gram positive diplococci present.

Final diagnosis:

1. Healed endocarditis (rheumatic) of the mitral valve.
2. Purulent salpingitis.
3. Acute bacterial endocarditis.
4. Meningo-encephalitis; embolic.

Comment: Unfortunately, no histological examination of the brain tissue was made. From studies on other cases, an embolic encephalitis in addition to the meningitis may be surmised. This is most likely in view of the convulsive seizure which immediately preceded admission to the hospital.

Case 4. C. R., white male. A 79-year-old Italian unable to speak English was admitted to the hospital on November 22, 1935, with the diagnosis of lobar pneumonia of the left lower lobe. During the hospital stay he failed to show any prolonged duration or great elevation of temperature, and he was discharged on 12–10–35. At this time the physical signs of consolidation were still present, and the diagnosis of unresolved pneumonia was made. On 12–19–35 he was re-admitted with the history of a febrile course since discharge and progressive loss of mental alertness.

Physical examination: Temperature 102°, pulse 96, blood pressure 95 mm. mercury systolic and 65 diastolic. An irrational, stuporous white male, lying flat in bed with marked dehydration of the skin and mucous membranes. The neck was rigid and quite painful to antero-posterior motion. There was present an area of tubular breathing in the left anterior axillary line extending from the fifth to the eighth rib. The heart rate was rapid with a regular rhythm. The cardiac tones were distant, but otherwise not remarkable. The spleen was not palpated, and the extremities were negative.

Laboratory data: *Urine:* negative for albumin, sugar or pathological sediment. *Blood:* hemoglobin 90 per cent; red blood cells 3,050,000; white blood cells 14,300; 90 per cent polymorphonuclear cells; 2 per cent eosinophile cells; 8 per cent lymphocytes. *Serology:* Wassermann test negative. *Spinal fluid:* 2,450 white blood cells: 96 per cent polymorphonuclear cells. *Culture:* blood, pneumococcus; spinal fluid, pneumococcus.

Immediately after admission a lumbar puncture was done and revealed a cloudy fluid under 320 mm. of pressure. The patient died about 24 hours after admission to the hospital.

Clinical diagnosis:

1. Unresolved lobar pneumonia.
2. Pneumococcic meningitis.
3. Pneumococcic septicemia.

Postmortem examination:

Autopsy diagnosis: Subacute ulcerative endocarditis of the mitral valves; organizing pneumonia in the mid-portion and lower part of the left lower lobe; multiple myocardial scars.

Brain: On gross examination the brain was covered with a thick creamy exudate. After sectioning the vessels appeared to be very much injected, and there was a thick purulent exudate with hemorrhagic ependymitis in the ventricles. In the medulla oblongata there was a small hemorrhage measuring 3 by 3 mm.

Histological examination: Purulent meningitis with gram-positive diplococci scattered throughout the exudate. There was a fairly large area of hemorrhage and exudate cells were seen in one area in the parenchyma of the brain-stem at the level of the upper part of the fourth ventricle. Numerous petechial hemorrhages were found scattered through the brain and cord. Multiple sub-ependymal petechial hemorrhages were noted and the ependyma was covered with purulent exudative cells.

Final diagnosis:

1. Unresolved lobar pneumonia.
2. Bacterial endocarditis, acute, pneumococcic of mitral valve.
3. Ependymitis.
4. Meningo-encephalitis, embolic.

Comment: The mental status of the patient and the presence of intercerebral hemorrhages, ependymitis and the exudation of white blood cells into the brain substances substantiate the presence of an encephalitis as well as a meningitis.

Case 5. J. M., white male, aged 24. On August 8, 1936, the patient was taking a motor trip. That night he complained of sore throat and of aching all over. On the following morning he developed a diarrhea and continued to complain of aching throughout his body and feeling badly. He was seen at this time by a physician who prescribed for him but without relief of his symptoms. About 11:00 a.m. of August 10, 1936, he suddenly became irrational and violent. He remained in this condition until he was admitted to the hospital.

Physical examination: Temperature 107.4°; pulse 160; respiration 30; blood pressure 110 mm. mercury systolic and 40 diastolic. A well developed, well nourished white male, lying flat in bed completely irrational and requiring a restraining sheet. The skin was hot and dry, but otherwise negative. There were large hemorrhages present in both retinae, and the neck was rigid. No pathological findings were present in the chest or lungs. A very harsh systolic and diastolic murmur were heard over the entire precordium. A bilateral positive Kernig reflex was present; the extremities were negative.

Laboratory data: *Blood:* red blood cells 5,385,000; hemoglobin 106 per cent; white blood cells 11,900; polymorphonuclear cells 88 per cent; lymphocytes 8 per cent; monocytes 3 per cent; myelocytes 1 per cent. *Serology:* Wassermann test negative.

Immediately after admission to the hospital a lumbar puncture was performed revealing a pink homogenous fluid under 800 mm. of pressure, containing 1,214 white blood cells; polymorphonuclear cells 94 per cent, lymphocytes 6 per cent. *Culture:* (8-11-36) spinal fluid, *Staphylococcus aureus;* blood culture, *Staphylococcus aureus.* The patient died about four hours after admission to the hospital without showing any essential changes in the original physical findings.

Clinical diagnosis:

1. Acute bacterial endocarditis of the aortic valve.
2. Meningitis.

Postmortem examination:

Autopsy diagnosis: Old healed ulcerative endocarditis of the mitral valves with superimposed verrucous endocarditis; old healed endocarditis of the aortic cusps with

superimposed verrucous endocarditis; firm splenic tumor (weight 425 grams) with multiple infarctions; embolic nephritis; multiple petechial hemorrhages in the skin and mucous membranes.

Brain: No postmortem examination.

Final diagnosis:

1. Healed endocarditis of the mitral and aortic valves.
2. Acute bacterial endocarditis (*Staphylococcus aureus*).
3. Subarachnoid hemorrhage.
4. Meningo-encephalitis, embolic.

Comment: In spite of the absence of a gross or histological examination of the brain, an assumption that this patient had an underlying embolic encephalitis in addition to the meningitis seems justified. The violent clinical onset, the hemorrhagic spinal fluid and the presence of embolic lesions of the spleen, kidney, skin and eye offer definite evidence to this effect.

Case 6. N. G., colored male, aged 27. For three weeks before admission on 5–8–37 this patient had been complaining of night sweats occurring some three to four times each week. These episodes were associated with a temperature elevation and chills lasting from one to two minutes. Since the onset of this illness his appetite had become poor, and he had had a general feeling of extreme weakness but was able to work as a truck driver up until 5–1–37. In addition to these symptoms, he also complained of palpitation of the heart and dyspnea over the past several months. On 5–3–37 he presented himself to the outpatient department and was referred from there to the hospital with a diagnosis of luetic heart disease, aortic regurgitation and possible bacterial endocarditis.

Physical examination: A well developed, and well nourished male who walked into the emergency room complaining of no acute pain and not appearing acutely ill. Temperature 101.6°, pulse 110, respiration 20, blood pressure 160 mm. mercury systolic and 70 diastolic. There were no pathologic findings on examination of the head, chest or lungs. The cardiac apex impulse was diffuse and over-active, and visualized in the fifth and sixth interspaces 12 cm. to the left of the mid sternal line. A systolic thrill was palpable over the apex. Percussion showed the left border extending 12 cm. to the left of the mid sternal line in the sixth intercostal space, and 5 cm. to the right. To and fro murmurs were heard over the aortic valve area and along the left sternal margin at the level of the fourth costal cartilage, and there was a blowing systolic murmur over the mitral area transmitted to the axilla. Examination of the peripheral vessels revealed a Corrigan pulse and pistol shot murmurs over both femoral arteries. The liver was palpated 3 cm. below the costal border, but the spleen was not palpable. The fingers showed a tendency to early clubbing.

Laboratory data: *Urine:* amber, alkaline, specific gravity 1.013, 1 plus albumin, 4–5 white blood cells and 3–4 red blood cells per high power field. *Blood:* (5–8–37) red blood cells 4,360,000; hemoglobin 89 per cent; white blood cells 28,700; 83 per cent polymorphonuclear cells, 14 per cent lymphocytes, 3 per cent monocytes. *Serology:* Kline and Wassermann tests positive. *Spinal fluid:* (5–19–37) 104 white cells, 89 per cent polymorphonuclear cells, 11 per cent lymphocytes; smear and culture were negative. *Blood culture:* (5–11, 5–18, 5–19) para-influenza bacillus.

On 5–19–37 the following note was made: "Patient has a stiff neck and complains of soreness in his muscles. He appears quite drowsy. A spinal puncture was done and a clear fluid was obtained." On 5–21–37 the spinal puncture was repeated and 5 c.c. of yellowish clear fluid removed. The pressure was 260 mm. of water. He died on 5–25–37.

Clinical diagnosis:

1. Luetic heart disease with aortic insufficiency.
2. Acute bacterial endocarditis.
3. Meningitis.

Postmortem examination:

Autopsy diagnosis: Ulcerative globular endocarditis of the aortic cusps superimposed on an old healed endocarditis; myocarditis; slight acute nonspecific aortitis; acute interstitial nephritis and early diffuse glomerulo-nephritis; anemic infarct of right kidney; scar of duodenal ulcer.

Brain: no examination.

Final diagnosis:

1. Old healed endocarditis of aortic cusps with superimposed ulcerative globular endocarditis.
2. Acute bacterial endocarditis (para-influenza bacillus).
3. Meningo-encephalitis, embolic.

Comment: The fundamental brain pathology here is probably an embolic encephalitis rather than a simple meningitis. The xanthochromic spinal fluid indicates damage to the cerebral vessels.

Case 7. D. S., colored male, aged 52, referred to the hospital because of irrational action and speech, shortness of breath and ankle edema. The present complaints had existed for three weeks prior to admission. The mental disturbance was further characterized by the obsession that inmates at the prison were trying to put poison in his food and medicine.

Physical examination: A well developed, fairly well nourished colored male, lying in bed with head and shoulders elevated. Respiration rapid and shallow. Temperature 99.2°, pulse 110, respiration 50, blood pressure 140 mm. mercury systolic and 50 diastolic. The neck veins were moderately distended and there was an area of bronchial breathing over the left apex. The cardiac rate was rapid, the rhythm regular, and the apex beat was present in the sixth intercostal space outside the mid clavicular line. A loud blowing to-and-fro murmur was present at the apex and a diastolic murmur was present over the base. The pulse was collapsing in type and Duroziez's sign was positive. On examination of the abdomen, the liver was palpable 4 cm. below the costal margin. There was definite pitting edema of both ankles and the fingers were clubbed. No abnormal neurological signs were noted.

Laboratory data: *Urine:* no pathological change. *Blood:* red blood cells 3,400,000; hemoglobin 65 per cent; white blood cells 15,500; polymorphonuclear cells 80 per cent, lymphocytes 20 per cent. *Serology:* Wassermann test negative. *Bacteriology:* blood culture negative; gram stain from heart valve showed short chain streptococci.

Clinical diagnosis:

1. Syphilitic heart disease with aortic insufficiency.
2. Subacute bacterial endocarditis.

Postmortem examination:

Autopsy diagnosis: Healed endocarditis of aortic cusp with presence of Aschoff bodies; superimposed globular ulcerative endocarditis; septic infarction of kidney; resolving pneumonia; sickle cell anemia.

Brain: The pia-arachnoid showed edema and was focally infiltrated with many cells of the large mononuclear type. In some areas were many plasma cells, es-

pecially around the blood vessels. The ganglion cell layer of the cortex was disorganized, and in some areas most of the cells were of the glial type. There was evidence of neuronophagia and the remaining ganglion cells showed increased pigmentation. One section showed a miliary abscess containing a central clump of what appeared to be a saprophytic growth and a small clump of cocci. Scattered through the sections there were many variously sized areas of softening without septic inflammatory reaction.

Final diagnosis:

1. Healed rheumatic endocarditis of the aortic valve.
2. Acute bacterial endocarditis.
3. Meningo-encephalitis, embolic.

Case 8. P. B., white male, aged 37. The patient was in normal health until three months before admission at which time he was living in Florida and began to have hard shaking chills followed by a fever at intervals of about seven days. This continued until June 1, 1937, and since that time he has had no recurrence. His general health during this time was apparently not impaired and he had no other complaint except for frequent, drenching night sweats and pain in his left elbow, right knee and right ankle which was present from April, 1937, until the time of admission to the hospital on June 18, 1937. There was a history of chancre and of a positive Wassermann test in 1935 with nine months of intramuscular and intravenous therapy. Rheumatic fever was diagnosed at the age of 14 years.

Physical examination: The patient was a fairly well developed and poorly nourished white male, lying quietly flat in bed complaining only of pain in the left elbow. Temperature 102.6°, pulse 100, respiration 20, blood pressure 90 mm. mercury systolic and 65 diastolic. The skin had a sallow appearance. No pathological findings were noted on examining the chest and lungs. The apex beat was 9.5 cm. to the left of the mid sternal line in the sixth intercostal space; the precordium was overactive, and a systolic thrill was present at the apex. There was a loud systolic and a short diastolic murmur over the apex transmitted widely over the precordium. On abdominal examination the liver was palpable 5 cm. below the right costal margin; the spleen was definitely palpable and non-tender. There was noted a slight tendency to clubbing of the fingers and toes.

Laboratory data: *Urine:* (6–19–37) cloudy, alkaline, specific gravity 1.030, negative for albumin and sugar; sediment negative for white and red blood cells. *Blood:* (6–19–39) red blood cells 3,550,000; hemoglobin 70 per cent; white blood cells 9,950; polymorphonuclear cells 77 per cent, lymphocytes 23 per cent. *Serology:* Wassermann test negative. *Blood cultures:* (6–19, 6–22 and 6–25) positive for *Streptococcus viridans.*

Clinically the patient showed no great change during his hospital stay until July 21, 1937, when he developed a stiff neck, became drowsy and showed signs of profound shock. Lumbar puncture was performed and 12 c.c. of bloody fluid removed. Smear and culture of the spinal fluid were negative. Following the spinal puncture the patient returned to his former mental status, the headache and cervical rigidity gradually subsided, and except for marked weakness the patient returned to his former clinical condition. On August 6, 1937, he was discharged to the City Home where he died on August 9, 1937. There was no necropsy.

Clinical diagnosis:

1. Rheumatic heart disease.
2. Subacute bacterial endocarditis.
3. Subarachnoid hemorrhage.
4. Meningo-encephalitis, embolic.

Comment: Whereas subarachnoid hemorrhage is the apparent diagnosis from the clinical and laboratory data given, the fundamental lesion is probably an embolic encephalitis. Unfortunately, he was not a patient in the hospital at the time of death, and no necropsy was performed.

Case 9. C. G., white male, aged 52. This man was in his usual state of health until January, 1937, seven months before admission to the hospital, when he began to complain of loss of weight, loss of appetite and inability to do his work. Two months before admission to the hospital he began to note the fact that his ankles would become stiff and swollen during the latter part of the day. During the latter part of May, some six weeks before admission, he developed a severe, rather sharp, intermittent and non-radiating pain in his left shoulder which was associated with a pain of similar nature over the lower left chest anteriorly. It was noted by his family physician that there was a definite friction rub over the region of this chest pain. These pains in the chest and shoulder lasted for a period of about four to six days. Otherwise his condition became progressively worse, the ankle edema failed to respond to bed rest or digitalis, and he was admitted to the hospital for further examination and treatment on July 1, 1937. No past history of rheumatic fever was obtained.

Physical examination: Temperature 100°, pulse 94, respiration 24, blood pressure 110 mm. mercury systolic and 55 diastolic. A somewhat undernourished white male with a sallow complexion, lying quietly in bed, mentally alert, rational and cooperative. Many grossly carious teeth were present. No pathological findings were noted in the chest. A systolic and diastolic murmur were heard over the aortic valve area and over the third left interspace at the sternal margin; a systolic murmur which was not transmitted was heard over the apex. No abdominal tenderness or mass was noted. The liver and spleen could not be palpated.

Laboratory data: *Urine:* (July 3, 1937), amber, acid, specific gravity 1.023, albumin and sugar negative; no white blood cells and only an occasional red cell seen. *Blood:* red blood cells 4,150,000; hemoglobin 70 per cent; white blood cells 7,500; polymorphonuclear cells 68 per cent, lymphocytes 31 per cent, monocytes 1 per cent. *Serology:* Wassermann test negative on two occasions. *Blood culture:* Eleven blood cultures were taken between the dates of June 9 and August 18, 1937, and all were reported negative.

On August 11, 1937, the spleen was palpable. Five days later the patient complained suddenly of very severe headache associated with nausea, the temperature rose suddenly to 102.8° and it was noted that the neck was moderately stiff. Examination of the fundi at this time was negative. A spinal puncture was done and 20 c.c. of hazy "ground-glass" appearing fluid under 150 mm. of pressure were removed. Laboratory examination of this fluid showed: white blood cells 540, polymorphonuclear cells 81 per cent, lymphocytes 19 per cent, Wassermann test negative, smear and culture negative. Immediately following this episode the patient was extremely drowsy and lethargic, but he gradually returned to his previous mental status and by August 27, 1937, was able to be up in a chair. He was discharged to the City Home on September 1, 1937, where he died 12 days later.

Clinical diagnosis:

1. Rheumatic heart disease.
2. Rheumatic endocarditis of the aortic valve.
3. Bacterial endocarditis.

Postmortem examination:

Anatomical diagnosis: Old healed endocarditis of the aortic valve with super-

imposed ulcerative endocarditis; cardiac hypertrophy and dilatation; healed infarct of the spleen; chronic passive congestion of the liver.

Brain: No postmortem examination.

Final diagnosis:

1. Healed endocarditis of aortic cusps (rheumatic).
2. Subacute bacterial endocarditis.
3. Meningo-encephalitis, embolic.

Case 10. H. W., colored male, aged 15. One week before the present admission on June 13, 1938, this young boy began to complain of a severe generalized headache and a constant dull pain over the back of his neck. Two days before admission he suddenly lost the use of his left arm and leg and, because this condition failed to improve, he was brought to the hospital. About six months prior to this occurrence he had been treated for acute rheumatic heart disease. The interval history was not eventful.

Physical examination: Temperature 103.2°; pulse 96; respiration 24; blood pressure 140 mm. mercury systolic and 10 diastolic. The general appearance was that of a poorly developed, emaciated colored male lying flat in bed complaining of pain in the back of the neck. There was a flaccid paralysis of the left arm and leg. The left side of the face was smooth and expressionless. Numerous petechial hemorrhages were present in both conjunctivae. There was no stiffness or tenderness of the neck, and the chest and lungs were normal. The cardiac apex was palpable in the fourth intercostal space in the mid axillary line with a palpable thrill in the region of the left nipple. A loud to-and-fro murmur was present over the entire precordium but loudest over the pulmonic valve area. A presystolic murmur was audible in the region of the left nipple. The spleen could not be palpated. In addition to the flaccid paralysis of the left arm and leg, a small petechial hemorrhage was present at the tip of the second finger of the left hand. The fingers were not clubbed.

Laboratory data: *Urine:* many red blood cells were noted on June 18, 1938. *Blood:* hemoglobin 52 per cent; white blood cells 17,100. *Chemistry:* formol-gel negative. *Spinal fluid:* white blood cells 45; polymorphonuclear cells 7, lymphocytes 38, culture negative. *Blood culture:* positive for *Streptococcus viridans.*

A lumbar puncture was done on June 16, 1938, and showed a clear fluid under normal pressure. There were present 45 white blood cells of which 38 were lymphocytes and 7 polymorphonuclear cells. On June 21, 1938, a beginning clubbing of the fingers was noted. Because no specific medication or treatment could be recommended he was discharged on July 17, 1938. On August 17, 1938, he returned to the hospital because of gangrene of the left foot and died August 18, 1938, the day following amputation.

Clinical diagnosis:

1. Rheumatic heart disease.
2. Rheumatic endocarditis of the mitral valve and aortic cusps.
3. Subacute bacterial endocarditis.
4. Left hemiplegia due to cerebral embolus.

Postmortem examination:

Anatomical diagnosis: Globular ulcerative bacterial endocarditis of the mitral valve and aortic cusps; aortic and mitral insufficiency; septic thrombosis of a branch of the mesenteric artery and infarction of the small intestine (ileum); multiple old and recent bland anemic infarctions of the kidney and spleen; thrombosis of a branch of the right coronary artery.

Brain: No postmortem examination.

Final diagnosis:

1. Rheumatic heart disease with chronic rheumatic endocarditis of the mitral valve and aortic cusps.
2. Subacute bacterial endocarditis.
3. Left hemiplegia due to cerebral embolus.
4. Meningo-encephalitis, embolic.

Comment: With the presence of an increase of white blood cells in the spinal fluid, it is probable that there were widespread embolic lesions of the brain and that the patient had a true embolic encephalitis as well as an arterial occlusion.

Case 11. V. S., white female, aged 18. Seven days before admission this patient developed a right sided headache associated with nausea, vomiting and mental confusion. These complaints had been preceded by an upper respiratory infection of about 10 days' duration. During an examination of the sinuses, ears and mastoids a stiff neck was noted and a tentative diagnosis of meningitis was made. A lumbar puncture revealed bloody fluid under pressure, and the patient was referred to the hospital with the diagnosis of a right frontal lobe tumor.

Physical examination: Temperature 102.8°; pulse 96; respiration 22; blood pressure 155 mm. mercury systolic and 40 diastolic. The general appearance was that of a fairly well developed and nourished individual in a confused semi-stuporous mental state. Grossly there was evidence of a flaccid paralysis of the left arm and leg and a left facial weakness of the central type. Nuchal rigidity was present. The chest and lungs were normal. The cardiac apex was palpated in the fifth intercostal space 11 cm. from the mid sternal line, and a loud to-and-fro murmur was audible over the entire precordium. The pulse was collapsing in type. The spleen was palpable. No clubbing of the fingers was noted. In addition to the left hemiplegia, the Kernig and Brudzinski reflexes were bilaterally positive, and the right abdominals were hyperactive.

A lumbar puncture done shortly after admission revealed a xanthochromic fluid under 265 mm. of pressure.

Laboratory data: *Urine:* 1–4 red blood cells per high power field. *Blood:* red blood cells 3,770,000; hemoglobin 64 per cent; white blood cells 20,650; polymorphonuclear cells, 86 per cent, lymphocytes 13 per cent, monocytes 1 per cent. *Spinal fluid:* white blood cells 77; polymorphonuclear cells 44; lymphocytes 43; culture negative. *Blood culture: Streptococcus viridans.*

Clinical diagnosis:

1. Rheumatic heart disease.
2. Chronic rheumatic endocarditis of the mitral and aortic valves.
3. Subacute bacterial endocarditis.
4. Left hemiplegia due to cerebral embolus.
5. Meningo-encephalitis, embolic.

Postmortem examination: none made.

Comment: The mental symptoms, nuchal rigidity and increase in the cellular elements of the spinal fluid point to widespread embolic lesions (embolic encephalitis) of the brain rather than simple arterial occlusion.

Case 12. E. S., white female, aged 53. This patient was brought to the hospital because of her inability to talk or to use her right arm and leg. For the past six to eight years she had not felt entirely well and for the past three to four years

this feeling had been characterized by shortness of breath on exertion, swelling of the ankles and easy fatigability. In February, 1935, two months before admission to the hospital, there were two acute episodes characterized by cough, dyspnea and cyanosis which were diagnosed as heart attacks. On the morning of admission, the patient was found in bed unable to talk or to move her right arm and leg.

Physical examination: Temperature 100°, pulse 110, blood pressure 134 mm. mercury systolic and 70 diastolic. A white female lying flat in bed, aphonic and unable to move her right arm or leg. The skin was pale with a suggestive café-au-lait tint and multiple petechiae were present. Moist râles were heard in both lung bases. A harsh systolic murmur replacing the first sound was present at the cardiac apex and followed by a loud snapping second sound. A systolic thrill was present over the apex. The spleen was not palpable. No clubbing of the fingers or toes was noted.

Laboratory data: *Urine:* albumin 2 plus; 10–15 white blood cells and rare red blood cell per high power field. *Blood:* hemoglobin 34 per cent; white blood cells 6,000. *Blood culture:* positive for *Streptococcus viridans.*

Diagnosis:

1. Rheumatic heart disease.
2. Chronic rheumatic endocarditis of the mitral valve.
3. Subacute bacterial endocarditis.
4. Cerebral embolus with right hemiplegia and aphonia.

Case 13. H. G., white female, aged 36. The patient had been in good health until four weeks before admission on September 12, 1934. Since this time she had complained of a dry cough, shortness of breath, soreness in her anterior chest, headache and a feeling of numbness in both hands. For several weeks she had been having frequent chills or chilly sensations. Three years ago she had had pneumonia which left her with a "weakened heart." Thereafter chills and coughing attacks had occurred frequently.

Physical examination: Temperature 104°, pulse 100, blood pressure 105 mm. mercury systolic and 65 diastolic. A well developed white female lying flat in bed but restless on account of a persistent hacking cough. The skin had a sallow appearance. A moderate degree of distention of the neck veins was present. Medium moist râles were heard in both lung bases. There was present a systolic murmur over the apex transmitted over the entire precordium and into the axilla. This murmur was harsh and rumbling in character and preceded by a presystolic murmur. The pulmonic second sound was accentuated. The liver was palpated 3 cm. below the costal margin. The fingers showed very early clubbing. The neurological examination and reflexes were negative.

Laboratory data: *Urine:* rare red blood cell. *Blood:* hemoglobin 84 per cent; red blood cells 4,600,000; white blood cells 8,600; polymorphonuclear cells 84 per cent, lymphocytes 15 per cent; monocytes 1 per cent. *Serology:* Wassermann negative. Blood culture: four cultures were reported negative.

On September 17, 1934, the patient suddenly had a severe chill and immediately thereafter developed a complete left hemiplegia.

Clinical diagnosis:

1. Rheumatic heart disease.
2. Rheumatic endocarditis of the mitral valve.
3. Subacute bacterial endocarditis.
4. Cerebral embolus with left hemiplegia.

Case 14. O. S., colored female, aged 18. Four weeks before entering the hospital on September 13, 1935, this patient developed a febrile illness which was charac-

terized by extreme weakness and headache. The temperature elevation was constant in nature, but there had been no chills. Two days before admission she developed severe, intractable pain in the upper portion of both thighs.

Physical examination: Temperature 102°, pulse 126, blood pressure 105 mm. mercury systolic and 55 diastolic. A well developed colored female, lying flat in bed complaining severely of pain in both thighs. There was marked pallor of the conjunctivae. The breath sounds in the left base were bronchovesicular in character. Both cardiac tones were loud and snapping in character, particularly the first. There was present a soft apical systolic murmur. The spleen could be palpated. There was an early clubbing of the fingers.

Laboratory data: *Urine:* trace of albumin; 15–20 red cells per high power field. *Blood:* red blood cells 2,710,000; hemoglobin 40 per cent; white blood cells 17,100. *Serology:* Wassermann test negative. *Blood culture: Streptococcus viridans.*

On December 1, 1935, she suddenly became unconscious, and on examination was found to have a complete right hemiplegia and multiple emboli to both fundi.

Clinical diagnosis:

1. Rheumatic heart disease.
2. Rheumatic endocarditis of the mitral valve.
3. Subacute bacterial endocarditis.
4. Cerebral embolus with right hemiplegia.

Case 15. M. B., colored female, aged 19. For two years prior to the present illness, this patient had been troubled with vague, transitory pains in both feet, ankles and hips which at times were associated with swelling of the feet. For two months before admission on April 2, 1936, she had noticed shortness of breath which at first occurred only after exertion, but later became so severe that she required two pillows to sleep comfortably.

Physical examination: Temperature 98°, pulse 105, respiration 36, blood pressure 120 mm. mercury systolic and 90 diastolic. A poorly nourished, emaciated colored female lying propped up in bed. The conjunctival mucous membrane was pale. On examination of the heart the apex beat was noted in the fifth intercostal space 11 cm. from the midsternal line, and it was forceful in character. A loud blowing systolic and diastolic murmur were heard over the mitral valve area. The systolic phase was noted over the entire precordium. The liver was palpable 1.5 cm. below the costal margin, and the spleen was firm and palpable. Marked clubbing of the fingers and toes was present.

Laboratory data: *Urine:* negative for red blood cells. *Blood:* red blood cells 3,510,000; hemoglobin 60 per cent; white blood cells 10,700; polymorphonuclear cells 76 per cent; lymphocytes 23 per cent; monocytes 1 per cent. *Serology:* Wassermann test strongly positive. *Blood culture: Streptococcus viridans.*

On April 21, 1936, the patient suddenly developed a complete left hemiplegia of the central type. She was discharged from the hospital three days later at the request of her husband.

Clinical diagnosis:

1. Rheumatic heart disease.
2. Chronic rheumatic endocarditis of the mitral and aortic valves.
3. Congestive heart failure.
4. Subacute bacterial endocarditis.
5. Cerebral embolus with left hemiplegia.

Case 16. R. M., white female, aged 22. The patient had been in good health until March 9, 1933, when she developed a severe pain in the left lower quadrant.

Seen by a physician at this time she was told that she was seven months' pregnant and had "pus tubes." On April 8, she was delivered of a stillborn infant and immediately thereafter began to show marked increase in temperature associated with chills and sweats. This state failed to improve with treatment and she was referred to the hospital on May 13, 1933.

Physical examination: Temperature 99°, pulse 100, respiration 20, blood pressure 110 mm. mercury systolic and 70 diastolic. Examination revealed a white female, well developed but poorly nourished and showing a definite pallor of the skin and mucous membranes. Medium moist râles were present over both apices. The cardiac impulse was palpated in the sixth intercostal space 13 cm. from the mid sternal line, and there was a systolic thrill over this region. The first sound at the apex was short and followed by a blowing systolic murmur. Over the pulmonic area the first sound was accentuated and reduplicated. On one occasion a gallop rhythm was noted. Definite clubbing of the fingers was noted, but the spleen could not be palpated and no petechiae were present. A large tender mass was felt in the left adnexia.

Laboratory data: *Urine:* trace of albumin; rare red blood cell. *Blood:* red blood cells 3,080,000; hemoglobin 55 per cent; white blood cells 18,300; polymorphonuclear cells 80 per cent, lymphocytes 18 per cent, eosinophiles 1 per cent, monocytes 1 per cent. *Serology:* Wassermann test negative. *Blood culture: Streptococcus viridans.*

On May 22, 1933, the patient suddenly developed left facial paralysis of the central type and definite weakness of the left arm and leg with positive clonus, Babinski and hyperactive deep reflexes on this side. A spinal fluid revealed a clear fluid under 220 mm. of pressure; white blood cells 48, polymorphonuclear cells 32, lymphocytes 16, Wassermann test negative. The culture on this fluid was not reported. The patient died July 6, 1933.

Clinical diagnosis:

1. Rheumatic heart disease.
2. Chronic rheumatic endocarditis of the mitral valve.
3. Subacute bacterial endocarditis.
4. Left hemiplegia due to a cerebral embolus.

Postmortem examination:

Anatomical diagnosis: Subacute vegetative endocarditis of the mitral valve; firm splenic tumor (weight 425 grams); anemic infarcts of the spleen and kidneys; embolic phenomena of skin; pulmonary tuberculosis.

Brain: No postmortem examination.

Final diagnosis:

1. Rheumatic heart disease.
2. Chronic rheumatic endocarditis of the mitral valve.
3. Subacute bacterial endocarditis.
4. Pulmonary tuberculosis.
5. Cerebral embolus with left hemiplegia.

Comment: The increase in the cellular elements of the spinal fluid indicates a more widespread embolic damage to the brain than simple arterial occlusion. It is our impression that histological study of the brain would have shown an embolic encephalitis.

Case 17. M. W., white female, aged 42. This patient was admitted to the hospital on July 2, 1934, with the history of having been in good health until July, 1933, at which time she had had 17 teeth extracted because of apical abscesses. Four days

later she fainted while going up a flight of steps, fell and fractured her skull in the frontal region. She was operated on for this three days later and has since this time suffered acutely with severe pain in this region. For two weeks prior to admission she had had a constant afternoon temperature, reaching a peak of 103°. She entered the hospital on the neurosurgical service.

Physical examination: Temperature 99.8°, pulse 85, respiration 20. No evidence of an operative type of lesion of the brain or skull was found after neurological examination, and the following observations were noted by the medical consultant. The skin and mucous membranes showed definite pallor with slight pigmentation of the skin typical of the café-au-lait tint. The cardiac apex was palpated in the fifth interspace 8.5 cm. from the midsternal line with a diastolic thrill present in this region. There was present here a diastolic murmur, and the first sound was loud and snapping. Over the pulmonic area the second sound was accentuated. The spleen was palpable 4 cm. below the left costal margin. Definite clubbing of both the fingers and toes was present.

Laboratory data: *Urine:* slight trace of albumin. *Blood:* hemoglobin 72 per cent; white blood cells 9,500; polymorphonuclear cells 81 per cent, lymphocytes 18 per cent, eosinophiles 1 per cent. *Blood culture: Streptococcus viridans.*

She was discharged from the hospital on July 5, 1934, and re-admitted on August 12, 1934, with complete left hemiplegia. She died on August 13, 1934.

Clinical diagnosis:

1. Rheumatic heart disease.
2. Chronic rheumatic endocarditis of the mitral valve and aortic cusps.
3. Subacute bacterial endocarditis.
4. Cerebral embolus with left hemiplegia.

Postmortem examination: Not made.

Summary

The fundamental pathologic change in the central nervous system in cases of bacterial endocarditis is a diffuse embolic meningo-encephalitis, and from this the various clinical manifestations arise. The types of lesions are pleomorphic and no local area of the brain appears to be predisposed to injury. As a consequence, the clinical neurologic manifestations are not absolutely predictable. There does occur, however, a broad pattern to which these signs adhere, and it is to this that we wish to direct special attention.

Meningitis: Of all the clinical manifestations of central nervous system damage, meningitis appears the most frequently. In varying degrees of severity it was noted in 11 of the 17 cases, and occurred most often and was most severe in cases of acute bacterial endocarditis. Nuchal rigidity and spinal fluid changes were common features of all. Opisthotonos, positive Brudzinski and positive Kernig's signs were sometimes present. Often the meningitis was present in conjunction with other neurological changes such as subarachnoid hemorrhage, hemiplegia as a result of gross arterial occlusion, hemorrhagic ependymitis and intra-ventricular hemorrhage. For the most part the cellular response showed a high percentage of polymorphonuclear cells, but in a definite number of instances lymphocytes and mono-

cytes predominated. In the cases of acute bacterial endocarditis, the organism responsible for the valvular lesion and present in the blood stream was recovered in four of six cases. In the cases of subacute bacterial endocarditis, the causative organism was not recovered in a single one of the five cases in which the spinal fluid was studied. A review of the literature confirmed this observation, and we were able to find reference to only one case [9] in which the *Streptococcus viridans* was recovered from the spinal fluid. This fact seems highly significant, and has led us to make very close and thorough investigation for the presence of a viridans endocarditis in all patients with a so-called " sterile meningitis " [5] which is not otherwise adequately explained.

Hemiplegia: Hemiplegia of a central type as a result of large cerebral emboli occurred in eight cases and was the next most frequent neurologic finding. This type of lesion was associated only with the subacute bacterial endocarditis cases. In three instances there was present also a meningitis, but in the remainder of the cases there was no clinical evidence of brain damage beyond the area supplied by the occluded artery. Aphonia accompanied the hemiplegia in only one instance.

In addition to these two outstanding clinical manifestations of central nervous system damage, the following changes were noted.

Subarachnoid hemorrhage: Gross blood in the spinal fluid was noted in three cases. This was present only in cases of acute bacterial endocarditis and was always associated with a meningitis.

Psychosis: A fully developed psychosis with delusions of persecutions was noted once. Clinically this was accompanied by a meningitis, and pathologically it was associated with a diffuse meningo-encephalitis.

Aphonia: This was present in one case and was associated with a hemiplegia as a result of a cerebral embolus.

Two patients were unconscious when admitted to the hospital, and two were irrational.

Headache, dizziness, auditory hallucinations, stupor, drowsiness and mental confusion occurred frequently in the symptomatology of the group.

Table 1 tabulates the neurologic signs and symptoms, and also lists the general physical signs occurring in the cases of bacterial endocarditis studied.

Spinal fluid: Examinations were made on the spinal fluid in 11 of the cases and the results are tabulated in table 2. For the most part these are self-explanatory. Consideration is given only to the pressure readings, the cytology and the bacteriological aspects as the other studies contributed no essential findings. In only one instance was the pressure elevated to an abnormal degree (Case 5). In this case the patient was violent, irrational and the victim of an overwhelming staphylococcic infection with a severe meningitis and subarachnoid hemorrhage. In three other cases pressure readings above 200 mm. were noted. The cellular response was varied in both degree and in character, and the cell counts ranged from 45 to 2,450 white blood cells per cubic mm. In character the cells for the most part showed a high

TABLE I

Case	Neurological		General Physical Signs	Neurological Diagnosis	Blood Culture
	Symptoms	Signs			
1 Acute bacterial endocarditis	None	Nuchal rigidity, spinal fluid *	Signs of valvular heart disease: absent Palpable spleen: not palpable (200 gm. post mortem) Clubbed fingers: present Skin and mucous membranes: negative	1. Meningo-encephalitis (post mortem)	Pneumococcus
2 Acute bacterial endocarditis	Headache, dizziness, auditory hallucinations	Lethargy, nuchal rigidity, spinal fluid *	Signs of valvular heart disease: present Palpable spleen: present Clubbed fingers: present Skin and mucous membranes: petechiae	1. Meningo-encephalitis 2. Subarachnoid hemorrhage 3. Intracerebral hemorrhage	Hemolytic streptococcus
3 Acute bacterial endocarditis	Convulsions	Loss of consciousness, nuchal rigidity, spinal fluid *	Signs of valvular heart disease: absent Palpable spleen: not palpable (280 gm. post mortem) Clubbed fingers: absent Skin and mucous membranes: negative	1. Meningo-encephalitis (post mortem)	Pneumococcus ?
4 Acute bacterial endocarditis	Stupor	Irrational, nuchal rigidity, spinal fluid *	Signs of valvular heart disease: absent Palpable spleen: absent Clubbed fingers: absent Skin and mucous membranes: negative	1. Meningo-encephalitis 2. Hemorrhagic ependymitis	Pneumococcus
5 Acute bacterial endocarditis	None	Irrational, violent, retinal hemorrhage, positive Kernig's sign, nuchal rigidity, spinal fluid *	Signs of valvular heart disease: present Palpable spleen: absent Clubbed fingers: absent Skin and mucous membranes: negative	1. Meningo-encephalitis 2. Subarachnoid hemorrhage (post mortem, no brain)	*Staphylococcus aureus*
6 Acute bacterial endocarditis	Headache, drowsiness	Drowsy, nuchal rigidity, spinal fluid *	Signs of valvular heart disease: present Palpable spleen: absent Clubbed fingers: present Skin and mucous membranes: negative	1. Meningo-encephalitis (post mortem, no brain)	Parainfluenza bacillus

* See table 2.

TABLE I—*Continued*

Case	Neurological		General Physical Signs	Neurological Diagnosis	Blood Culture
	Symptoms	Signs			
7 Subacute bacterial endocarditis	None	Delusions of persecution	Signs of valvular heart disease: present Palpable spleen: absent Clubbed fingers: present Skin and mucous membranes: negative	1. Meningo-encephalitis (post mortem)	Short chain gram positive streptococcus
8 Subacute bacterial endocarditis	Headache	Nuchal rigidity, spinal fluid *	Signs of valvular heart disease: present Palpable spleen: present Clubbed fingers: present Skin and mucous membranes: café-au-lait	1. Meningo-encephalitis 2. Subarachnoid hemorrhage	*Streptococcus viridans*
9 Subacute bacterial endocarditis	Headache	Stupor, nuchal rigidity, spinal fluid *	Signs of valvular heart disease: present Palpable spleen: present Clubbed fingers: absent Skin and mucous membranes: pallor	1. Meningo-encephalitis (post mortem, no brain)	Negative repeated
10 Subacute bacterial endocarditis	Headache, loss of use of left arm and leg	Hemiplegia, spinal fluid *	Signs of valvular heart disease: present Palpable spleen: absent Clubbed fingers: absent Skin and mucous membranes: negative	1. Meningo-encephalitis 2. Cerebral embolus (post mortem, no brain)	*Streptococcus viridans*
11 Subacute bacterial endocarditis	Headache, confused	Stuporous, hemiplegia, left, nuchal rigidity, spinal fluid *	Signs of valvular heart disease: present Palpable spleen: present Clubbed fingers: absent Skin and mucous membranes: negative	1. Meningo-encephalitis 2. Cerebral embolus (left)	*Streptococcus viridans*
12 Subacute bacterial endocarditis	None	Aphonia, hemiplegia, right	Signs of valvular heart disease: present Palpable spleen: absent Clubbed fingers: absent Skin and mucous membranes: café-au-lait, petechiae	1. Cerebral embolus	*Streptococcus viridans*

TABLE I—*Continued*

Case	Neurological		General Physical Signs	Neurological Diagnosis	Blood Culture
	Symptoms	Signs			
13 Subacute bacterial endocarditis	Headache	Hemiplegia, left	Signs of valvular heart disease: present Palpable spleen: absent Clubbed fingers: present Skin and mucous membranes: café-au-lait	1. Cerebral embolus	Negative
14 Subacute bacterial endocarditis	Headache	Hemiplegia, right	Signs of valvular heart disease: absent Palpable spleen: present Clubbed fingers: present Skin and mucous membranes: pallor	1. Cerebral embolus	*Streptococcus viridans*
15 Subacute bacterial endocarditis	None	Hemiplegia, left	Signs of valvular heart disease: present Palpable spleen: present Clubbed fingers: present Skin and mucous membranes: pallor	1. Cerebral embolus	*Streptococcus viridans*
16 Subacute bacterial endocarditis	None	Hemiplegia, left, spinal fluid *	Signs of valvular heart disease: present Palpable spleen: absent Clubbed fingers: present Skin and mucous membranes: pallor	1. Cerebral embolus	*Streptococcus viridans*
17 Subacute bacterial endocarditis	Frontal headache	Hemiplegia, left	Signs of valvular heart disease: present Palpable spleen: present Clubbed fingers: present Skin and mucous membranes: café-au-lait	1. Cerebral embolus	*Streptococcus viridans*

TABLE II

Case No.	Type	W.B.C.	P.M.N.	Lymphs	R.B.C.	Pressure	Culture
1.	Acute bacterial endocarditis	1200	96%	4%	0	175	Negative
2.	Acute bacterial endocarditis	403	88%	12%	1650		*Streptococcus hemolyticus*
3.	Acute bacterial endocarditis	150	90%	10%			Gram positive diplococci (smear)
4.	Acute bacterial endocarditis	2450	96%	4%			Pneumococcus
5.	Acute bacterial endocarditis	1214	94%	6%	Gross	800	*Staphylococcus aureus*
6.	Acute bacterial endocarditis	276	73%	27%		260	Negative
8.	Subacute bacterial endocarditis				Gross		Negative
9.	Subacute bacterial endocarditis	540	81%	19%		150	Negative
10.	Subacute bacterial endoacrditis	45	7	38			Negative
11.	Subacute bacterial endocarditis	77	33	44		265	Negative
16.	Subacute bacterial endocarditis	48	32	16		220	Negative

percentage of polymorphonuclear leukocytes, but in some instances the lymphocytes showed a marked predominance. This was in keeping with pathologic findings in which areas of monocytic meningitis were often found associated with areas of polymorphonuclear cell infiltration. The bacteriological studies have already been discussed.

Conclusions

1. The fundamental brain pathology in bacterial endocarditis is a diffuse embolic meningo-encephalitis.

2. Embolic brain lesions are an important part of the pathologic anatomy of bacterial endocarditis, and frequently produce the outstanding clinical features of the syndrome.

3. The presence of a "sterile meningitis" in any case of an obscure febrile illness should always suggest the possibility of a viridans endocarditis.

4. The triad of clubbed fingers (Hippocratic), splenomegaly, and meningo-encephalitis is presumptive evidence of acute bacterial endocarditis in spite of the absence of signs of cardiac lesions.

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TUBERCULOSIS AMONG STUDENTS AND GRADUATES OF MEDICINE*

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The problem of tuberculosis among students and graduates of medicine has been present since the earliest days of medical practice. Valsalva, the anatomist (1666–1723), avoided postmortem examinations when the cause of death was consumption. Morgagni, his pupil (1682–1771), continued this practice avoiding them in order to protect his students as well as for personal reasons. Isocrates (436–338 B.C.), Aristotle (384–322 B.C.), and Galen (131–201 A.D.) appreciated the contagiousness of tuberculosis. Laennec, himself, infected his left index finger while performing a postmortem examination about 1800 and died of consumption in 1826.

In 1818 Armstrong said: "When young men enter upon the study of medicine, they occasionally break up their general strength by the intensity of their applications in the dissecting rooms, in the tainted air of a hospital, or in their own apartments, and may actually become consumptive from this cause." Long before and ever since Armstrong made this statement, similar factors have been cited to account for tuberculosis among medical students and physicians. We now assign the cause of diphtheria to the diphtheria bacillus and have relegated to the discard all the opinions of the past. We have equally good reason to assign the cause of tuberculosis to the tubercle bacillus. Of the secondary factors which are so freely discussed, we are not certain of one.

Because of the rapid decline of tuberculosis in the general population, the disease among physicians as well as other members of hospital personnel has become more conspicuous. Moreover, modern aids in diagnosis have enabled physicians to diagnose the disease in its clinical forms months and even years before physicians of two or three decades ago could possibly have recognized it. Even the first infection type of tuberculosis may often be detected as to location in the living if adequate examination is made; whereas, only a short time ago this type of tuberculosis was located only at postmortem examination.

In a few medical schools, observations have been made on the incidence of tuberculin reactors among the students. For example, in 1931 Hetherington et al. tested 452 medical students at the University of Pennsylvania and compared the findings with those of high school boys in Philadelphia.

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In the high school group they found 77.8 per cent reacted to the tuberculin test but in the medical school group the incidence of reactors was 93.6 per cent. In the senior medical class, however, 98.2 per cent of the students reacted to tuberculin. Herman et al. found that 79 per cent of the first year medical students at Johns Hopkins University reacted to tuberculin as compared to approximately 100 per cent of students in the third and fourth years. These and other reports have indicated that the infection attack rate among students of medicine is high.

Demonstrable lesions in medical students and physicians have also been investigated in recent years. Soper and Amberson state that at the Yale school of medicine, tuberculosis has not been a major problem. Among 427 students who entered the school from 1930 through September 1937, six had parenchymal lung lesions on entrance; three developed minimal apical lesions; one subapical disease; and two fell ill during their course. Thus, they conclude that six of the twelve students who had clinical tuberculosis possibly contracted infection or superinfection during the medical course. The situation existing in other schools of medicine as obtained through correspondence with Student Health Services, physicians, etc., is also reported. In summarizing this work on medical students, Soper and Amberson state: "They are, as a rule, less rapidly and less certainly infected than pupil nurses, but they still acquire infection to an excessive degree. The morbidity among them appears to vary. It seems alarmingly high in a few instances, but not in the majority of schools whose figures are known. Many of the leading schools have already instituted programs of prevention and case finding. Where a definite program is lacking there is an increasing consciousness of the problem and effort to cope with it. The mortality seems not unduly high, probably because the cases developing are apt to be diagnosed and treated early."

Chadwick's observations led him to state that "There is a much higher incidence of tuberculosis among nurses, medical students and doctors during their first years of practice than in the general population."

Vaucher et al. of the University of Strasbourg began making examinations of students in 1929. They observed several students who became tuberculin reactors soon after ward work was begun and described the ensuing demonstrable lesions, noting the absence of symptoms in the majority of cases. In discussing this paper, Rist of Paris pointed out that his experience with many students confirmed that of Vaucher and that at the University of Minnesota.

Scheel of Oslo observed medical students between 1926 and 1936. The annual morbidity rate was 4.8 per cent among those who entered school as non-reactors to tuberculin, and 1.1 per cent among those who entered as reactors. The morbidity rate among the non-reactors compared with the reactors was 4 to 1. He found that the maximum tuberculosis morbidity and mortality are observed during the first three years after primary infection, chiefly

during the first year. The morbidity from pleurisy is 9 per cent during the first year.

Jacob in discussing the first infection type of tuberculosis points out the difficulty in differentiating it from the reinfection type in the absence of tuberculin tests as follows: "In fact, neither by the seat of the lesion, nor by its radiological appearance does a primary tuberculosis infection essentially differ from reinfection. The author therefore believes that so long as one does not investigate and register regularly and periodically the results of the tuberculin test in the school, the army, the factory, the shops and the colleges, the notion of primary infection however interesting, will not become a clinical fact which must be taken into account when establishing a prognosis or deciding upon a course of treatment. Clinical investigation does not enable one to differentiate with certainty or even with much probability a primary tuberculosis infection from a re-infection."

Hetherington et al. found that evidence of disease at the apices of the lungs increased definitely from year to year among medical students. Among the freshmen in only 4.1 per cent was such evidence revealed. This percentage increased to 11.6 in the junior year and 20.5 in the senior year.

Pepper in discussing the incidence of tuberculosis among medical students at the University of Pennsylvania as reported by Hetherington et al. states: "Our students handle specimens removed at autopsies made on tuberculous patients. Very much of our clinical teaching is done at the Philadelphia General Hospital which cares for a large number of tuberculous patients. But our medical students do not seem to be more liable to other ailments than the rest of the university students." In commenting on Dr. Pepper's presentation Harvey says: ". . . that it is time for us, as an Association (Association of American Medical Colleges) and for our schools individually, to pay more attention to the health of students. Clearly, it is time to do so, for neglect of the student's health is lamentable in the college and it becomes almost criminal in a medical school."

Lees says: "The problem of tuberculosis among medical students at the University of Pennsylvania has been given special study and consideration during the past three years by a faculty committee appointed by Dean William Pepper. The prevalence of the disease among our students of medicine has been significantly greater than that encountered in students of other schools on the campus. Moreover, the development of new lesions has been observed chiefly in members of the third and fourth year classes. The distribution of cases in the clinical years of training as contrasted with the non-clinical years, approximately eight to one, has followed much the same pattern during the past five years. However, the incidence of tuberculosis of the reinfection type among medical students has fallen from 5.8 per cent in the school year 1935–1936 to 3.9 per cent at the present time. During this period various procedures have been planned with the idea of reducing to a minimum the student's opportunity for infection with tubercle bacilli. The use of tuberculous patients for second year classes in physical diagnosis has

been discontinued. The department of pathology has carefully revised the technic employed in the autopsy room and gives systematic instruction to students regarding the hazards of various types of infections from laboratory sources. In the tuberculosis clinics conducted by the department of medicine, a very limited number of positive sputum cases are used for demonstration purposes and the conduct of patient and student is carefully supervised. In view of the fact that approximately 90 per cent of our medical students are allergic to tuberculoprotein at the beginning of the third year and since the development of pulmonary tuberculosis reaches its peak in the particular age zone represented by a majority of this group, it would seem mandatory that every possible protection should be given the student against possible infection with tubercle bacilli."

In the report from the Central State Hospital at Indianapolis, Indiana, for 1932 the following statements are made: "Since 1896 all the autopsies were performed in the large amphitheater, which is also used for clinical instruction of medical students, nurses, and social workers. During the performance of every autopsy on patients who died of an infectious disease such as miliary or pulmonary tuberculosis, streptococcic septicemia, typhoid fever, there is a certain spreading of infectious organisms. It is practically impossible to disinfect safely the autopsy table and its immediate surroundings after every autopsy. In the interest of the students who receive clinical instruction in the amphitheater we removed the autopsy table to other quarters, since in our opinion the postmortem table and its surroundings constitute at times a distinct health hazard." The pathologist and director of research of this institution, Dr. Walter L. Bruetsch, had been convinced that at least some of the tuberculosis among students was due to infection from the postmortem room.

Bates found that 7.1 per cent (239) of 3,349 patients discharged from the Trudeau Sanatorium between 1916 and 1931, were medical students and physicians. Of these, only a slightly greater proportion had their disease detected earlier than those engaged in other activities of life. This is not surprising when one considers that between 1916 and 1931 routine tuberculin tests were not administered to adults and the roentgen-ray film was employed mostly as a confirmatory measure, that is, after symptoms were present or physical signs were elicited. Significant symptoms usually mean moderate or far advanced disease. With routine and periodic tuberculin testing and roentgen-ray film examinations now in practice among medical students, one rarely sees a diagnosis first made after the disease is advanced.

There are reports in the literature which show a low incidence of clinical tuberculosis among physicians. For example, Laird records 57 physicians who have been employed at the Nopeming Sanatorium, six of whom were tuberculous before entering the service; three who began the service as nonreactors later reacted to tuberculin; one other physician after leaving the sanatorium had a pulmonary hemorrhage. Pollock and Forsee found only 1.7 per cent of 227 physicians developed clinical tuberculosis. Space does

not permit us to present all of the papers and discussions that have appeared on this subject. However, we have included in the reference list the more important ones known to us.

The nature of tuberculosis dictates that any conclusive statement about it must be based on a period of observation long enough to include its entire evolution, which is the span of life. Therefore, the only way to determine the seriousness of the problem with any degree of accuracy is to start with the students as they enter the school of medicine and follow them carefully throughout life. This is a relatively simple matter as long as they are students, interns, and resident physicians in hospitals but it becomes a difficult matter to keep in touch with all of them after they locate in various parts of the world. Some will neglect or refuse to answer questionnaires, because of fear of publicity. Indeed, the physician who develops tuberculosis usually does not want any one to know about it except his personal physician.

We have attempted to trace the 1,894 students who graduated or were scheduled to graduate from the school of medicine of the University of Minnesota from 1919 to 1936 inclusive. Group I includes 1,441 students who were in the graduating classes from 1919 to 1932 inclusive, and Group II includes the 453 students who were in the classes graduating from 1933 to 1936. Prior to 1929, when the class graduating in 1933 entered the university, no special routine examinations for tuberculosis were made, consequently our information on Group I was obtained largely through questionnaires. Although we knew of the majority of students who fell ill from tuberculosis while in school, as well as those who had since fallen ill, the questionnaires added more cases to this list. While the response to our questionnaires was a manifestation of splendid coöperation on the part of the former graduates of this school of medicine, we were unable to secure information concerning 7.5 per cent of this group. The carefully outlined program of examinations for tuberculosis among our medical students since 1929 has provided us with information on infection attack rate, appearance of lesions by roentgen-ray film, symptoms, etc. in Group II.

In the classes of 1919 to 1936, we know of 35 deaths from causes other than tuberculosis. Of the remaining 1,859, 90 per cent replied to the questionnaire. In Group I, the leading non-tuberculous illness reported was pneumonia with 42 cases; this was followed by 28 cases of appendicitis, and 13 cases of scarlet fever. In all, 242 individuals reported serious illness from a total of 68 different disease entities. In Group II, of the 369 who replied to our inquiries, 49 have had major non-tuberculous illnesses caused by 28 disease entities. In this group also, pneumonia, appendicitis and scarlet fever were the leading causes of these illnesses.

Group I

The total number of replies from the members of the classes of 1919 to 1932 was 1,304. All deaths from tuberculosis are included in this number.

In the letters sent to this group, the following questions were asked:

1. Did you suffer from pleurisy with effusion or tuberculosis in any form while in school?
2. Have you had any form of tuberculosis since graduation?
3. Do you know of other members of your class who have been ill from, or have died of tuberculosis in school or since graduation?
4. Do you react to the tuberculin test? If so, how long have you been a reactor?
5. Have you had a roentgen-ray film examination of your chest recently? If so, did it reveal any abnormal shadows?
6. Have you had any other serious illness since graduation?

Forty-one (3.14 per cent) stated that they developed clinical tuberculosis while in school. Ten others reported having had pleural effusions as students and five others stated that they had tuberculosis before entering medical school. Thus, 51 (3.91 per cent) of this group developed clinical tuberculosis, including pleurisy with effusion, during their years in medical school before graduation.

Eliminating the five individuals who developed clinical tuberculosis prior to entering medical school and the 51 others who developed tuberculosis while in school, 41 of the remaining 1,248 graduates (3.29 per cent) including four cases of pleural effusion, reported that they developed tuberculosis after graduation from medical school.

Exclusive of the five developing tuberculosis before entering medical school, 92 (7.07 per cent) have had clinical disease while in school or since graduation. Of these, 11 (0.85 per cent) have died of tuberculosis.

Concerning tuberculin reactions, 389, or 29.9 per cent, have either had no tests or do not remember the results. Of the remaining 915 reporting, 655, or 71.6 per cent, stated that they had positive reactions to tuberculin while 260, or 28.4 per cent, reported negative reactions. The 655 positive reactions were broken down according to the time at which they were acquired. Two hundred and thirty-four (35.7 per cent) did not know when they became reactors. Eleven were dead, of whom one replied before death. Of the remaining 411 reactors, 140 (34.0 per cent) became positive before entering the medical school; 207 (50.4 per cent) became reactors while in medical school; and 64 (15.6 per cent) became reactors after graduation.

The percentage of persons recorded as reactors to tuberculin varied from 15 to 33 until 1925, whereas the percentage of graduates who either had no tests or did not remember ran from 46 to 62 during this same period. In 1925 a tuberculosis service was made compulsory and in 1929 routine annual testing of all medical students was begun. The number reporting reactions had risen sharply since that time while the number who have not been tested or do not remember has shown a correspondingly sharp decrease. The 1932 class recorded 85 per cent reactors and only 3 per cent no test (table 1).

TABLE I

Summary of Data Obtained by Questionnaire for Group I

Year	Number of Graduates	Dead (non-tuberculous)	Total Replies	Dead of Tuberculosis	Tuberculosis in School	Tuberculosis Since School	Tuberculin Reaction						Number Having Recent Chest Examination
							Became Reactors				Non-reactors	No Test	
							Before School	In School	After School	Unknown			
1919	59	1	55		2	2	2	0	4	5	14	30	25
1920	92	5	79	3	4	4	5	0	5	12	17	37	32
1921	81	1	73		3	1	1	4	5	7	15	41	32
1922	76	3	69		3	2	2	0	2	6	16	43	30
1923	78	4	69		2	0	1	2	4	5	14	33	35
1924	102	3	92	3	3	6	2	6	5	18	16	41	51
1925	90	2	79		5	0	6	6	0	15	15	37	40
1926	107	5	96	1	5	2	3	5	5	27	26	29	53
1927	103	1	95	1	6	4	7	9	4	26	17	32	46
1928	120	1	109		3	2	8	18	4	27	28	24	57
1929	134	2	120	1	2	3	11	27	8	26	34	14	69
1930	126	0	114		3	8	29	32	8	17	19	9	69
1931	129	2	118	2	5	4	24	41	3	20	13	15	74
1932	144	1	136		5	3	39	57	7	13	16	4	96
Total	1441	31	1304	11	51	41	140	207	64	234	260	389	709

We also were interested in determining as far as possible the time at which these physicians became reactors. The percentage that did not know this time ran close to 60 until 1926; since then it has declined steadily.

Seven hundred and nine (55 per cent) of those who replied reported that they had recent roentgen-ray examinations of the chest. The data show a steady increase over the years in the proportion of graduates having regular chest examinations including roentgen-ray films. In the 1919 class this percentage was 45 while in the 1932 class it was 70.

The total 92 individuals in Group I who reported having had clinical tuberculosis in some form approximates an entire class of our school of medicine. The eleven who died represent 26.2 per cent of the total number of deaths from all causes.

Group II

The 453 students who entered the School of Medicine from 1929 to 1932 inclusive, that is, in the classes graduating from 1933 to 1936 inclusive, were carefully examined throughout their enrollment in the School of Medicine. All the members of the class entering in 1929 were tested with tuberculin and all had roentgen-ray films of the chest annually regardless of the tuberculin reaction. The non-reactors on entrance were retested annually unless they became reactors. The members of the other three classes had the tuberculin test administered on entrance and annually or more often thereafter as long as they were non-reactors. In these classes roentgen-ray films of the chest were made only of the tuberculin reactors on entrance and annually thereafter and those who became reactors under our observation and annually thereafter unless shadows appeared, following which films were made more frequently. Four of the 453 have died of non-tuberculous conditions. The remaining 449 are included in this report.

Table 2 shows that in these classes on entrance the percentage of reactors to tuberculin ranges from 33.3 to 37, while on graduation the range is from 57.7 to 77.9 per cent. The average in the four classes, table 3, is 35.6 per cent on entrance to the School of Medicine, 41 per cent at the end of the third year, and 67 per cent at the end of the fourth year, and 50.2 per cent of those who reacted negatively to tuberculin upon entrance to the medical school became positive before graduation.

In figure 1, we have illustrated graphically the percentage of tuberculin reactors among medical students over the four-year period, while in figure 2 we have shown the total percentage of reactors on entrance, at the end of the third year, and on graduation. While there was an increase of reactors between entrance and the end of the junior year, it was greater during the senior year when the students had more contact with tuberculous patients. Of the 449 students in this group, 160 (35.6 per cent) reacted to the test on entrance, 145 (32.3 per cent) became reactors while in school, and 144 (32.1 per cent) were non-reactors on graduation.

The questionnaire sent to those who were recorded as reactors on graduation included this question: "Our records show that you reacted to the tuberculin test on graduation. Is this correct?" That sent to those who were recorded as non-reactors on graduation included the following questions: "Our records show that you did not react to tuberculin during the senior year. Is this correct? If so, have you become a reactor since graduation? If so, when and under what circumstances?"

From these replies, we learned that some students had tuberculin tests administered in various clinics during the latter part of their senior year, which were not reported to the Health Service. Thirteen reported that they

TABLE II

Comparison of Percentages of Infected Medical Graduates during Course of Study: on Entrance, the End of the Third Year, and the End of the Fourth Year of Medical School, Shown by Classes.

Class Graduating Year	Total in Class	Reactors Entrance		Reactors End Third Year		Reactors End Fourth Year	
		No.	Per Cent	No.	Per Cent	No.	Per Cent
1933	78	26	33.3	33	42.3	45	57.7
1934	127	47	37.0	52	40.9	79	62.2
1935	113	39	34.5	46	40.7	79	70.0
1936	131	48	36.6	53	40.5	102	77.9

TABLE III

Comparison of Percentages of Infected of 449 Medical Graduates during the Course of Study: on Entrance, the End of the Third Year, and the End of the Fourth Year of Medical School.

Number of Graduates	Reactors Entrance		Reactors End Third Year		Reactors End Fourth Year		Per Cent of Non-Reactors Who Became Reactors
	No.	Per Cent	No.	Per Cent	No.	Per Cent	
449	160	35.6	184	41.0	305	67.8	50.2

were definite reactors on graduation, which we had recorded as non-reactors, and 10 reported that they are definitely non-reactors, while our records show one mild reaction in each case. Since no subsequent reaction occurred in these 10 physicians, it is probable that our interpreters had over-read the tests. In each case we have accepted the statement of the graduate concerned. On this basis, 305 (67.9 per cent) graduated as reactors and 144 (32.1 per cent) as non-reactors.

Replies have been received from 369 of the 449 graduates in this group. Of these 102 were from physicians who did not react to tuberculin at the end of the senior year. Sixty-five of these have had tuberculin tests since graduation, among whom 30 (46.2 per cent) became reactors as interns, 15 (23.0 per cent) became reactors following their internships, 20 (30.8 per cent) are still non-reactors.

Although few of these graduates took internships in hospitals which required tuberculosis services, practically all were in hospitals where they were exposed to the unsuspected contagious case of tuberculosis admitted for some other co-existing condition. Moreover, most of these hospitals do not examine the members of their own personnel. Certainly to allow 46.2 per cent of uninfected interns to become infected during their hospital services constitutes a serious problem in tuberculosis control. From our own observations among these physicians while they were students, together with

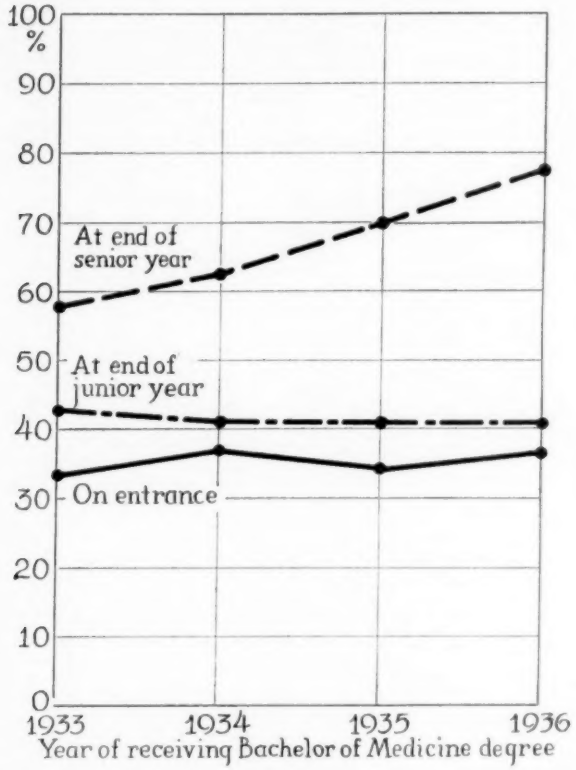

FIG. 1. Percentage of positive tuberculin reactors among medical students.

their replies to our questionnaires, we now know of a total of 350 (78.2 per cent) who are reactors to tuberculin.

Students in the College of Education, the control group, came from the same general section of the country and while in school lived in the same general environment as the students of medicine except that they were not brought in direct contact with tuberculous patients as a part of their work. On entrance to the College of Education 24.8 per cent of the students reacted to tuberculin, while on graduation 28.5 per cent reacted (figure 2). Thus, only slightly more than 1 per cent of the non-reactors became infected each year. Apparently in this community the infection attack rate is only about

1 per cent per year, as indicated by the findings in this group of students in the College of Education and the work of Stewart on children.

The following questions were included in our questionnaire:

"Have you had pleurisy with effusion or tuberculosis in any form, since graduation? Have you had roentgen-ray film examination of your chest recently? If so, did it reveal any abnormal shadow? Have you had any other serious illness since graduation? Do you know of any other members of your class who have been ill from or have died of tuberculosis, either in

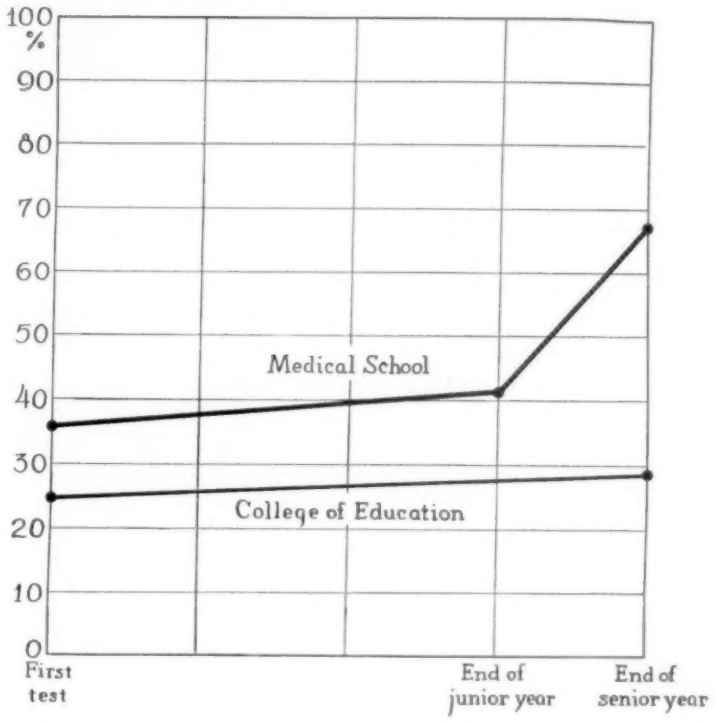

FIG. 2. Percentage of positive tuberculin reactors among students over four year period.

school or since graduation?" Three hundred and sixty-nine (82.2 per cent) of the graduates of these four classes replied and 291 (78.9 per cent) of those who had reacted to tuberculin have had recent roentgen-ray examinations of their chests.

GROUP II STUDENTS WHO DEVELOPED PRIMARY TUBERCULOSIS COMPLEXES BEFORE ENTERING MEDICAL SCHOOL

On entrance to the school of medicine there were 160 students in the classes of 1933–36 inclusive who had already developed primary complexes as manifested by the tuberculin reaction.

A. *Those Who Had New Lesions Demonstrated while in School*

In the fall of 1929 this student entered the school of medicine as a tuberculin reactor. In January 1930 films of his chest were clear. In March 1930, he had an effusion in the right pleural cavity but no evidence of disease could be seen in either lung. In February 1935, definite disease was demonstrated in both upper lobes. In February 1936, the disease in the right lung had increased but we have been unable to locate him since that date.

This student entered medical school in 1932 as a tuberculin reactor. There was evidence of a primary complex in the right lung and diaphragmatic adhesions on the right side. In 1933 he had renal tuberculosis and tuberculous epididymitis on the left side; these were treated surgically in 1934. In May 1936 he had pleural effusion on the left side. This physician is now practicing medicine.

B. *Those Who Had New Lesions Demonstrated since Graduation*

In the fall of 1929, when this student entered the medical school he was a reactor to tuberculin. In January 1930 there was evidence of calcium deposits in both hilum regions. In the spring of 1936 while practicing medicine, he had a pulmonary hemorrhage and a definite area of disease was found in the right upper lobe. He was in a sanatorium approximately six months, following which he remained inactive at home. The roentgen-ray shadow diminished definitely in size and he returned to work in the spring of 1937. At present he is practicing medicine.

In the fall of 1932, on entrance to the medical school, this student reacted to tuberculin. Roentgen-ray films of the chest throughout his medical course were clear. In February 1937 he developed pleurisy with effusion on the right side. Although this was diagnosed clinically as tuberculosis, tubercle bacilli were not recovered from the fluid.

In the fall of 1932, this student of 28 years entered the School of Medicine as a tuberculin reactor. Roentgen-ray films of his chest revealed evidence of a primary complex in the left lung and hilum. He completed his internship in 1936 with no change in the roentgen-ray film examination and with no symptoms of tuberculosis. He then entered the practice of medicine and was apparently healthy until December 1938, when he had an attack of bronchitis and complained of fatigue. On January 6, 1939, a roentgen-ray film was made of his chest which revealed definite evidence of disease involving the greater part of the upper half of the right lung in addition to the evidence of the primary complex in the left lung hilum. He was admitted to a sanatorium, where he is now being treated by artificial pneumothorax.

Thus, among 160 students who had primary tuberculosis complexes in their bodies on entrance to the school of medicine, we know of five (3.1 per cent) who have had diagnoses of clinical tuberculosis (table 4).

TABLE IV

School of Medicine

160 with primary complex on entrance
- *a*. Lesions detected while in school, 2
- *b*. Lesions after graduation, 3

} (3.1 per cent)

145 developed primary complex in school
- *a*. Lesions detected while in school, 11
- *b*. Lesions after graduation, 3

} (9.6 per cent)

45 developed primary complex after graduation
- Lesions detected, 5

School of Education

686 reactors
- Lesions detected while in school, 3 (0.44 per cent)

Group II Students Who Developed Primary Tuberculosis Complexes while in School

One hundred and forty-five students in Group II developed the primary tuberculosis complex as manifested by the tuberculin reaction while in school. In some of these cases the location of lesions became demonstrable before or after graduation.

A. *Those Who Had New Lesions Demonstrated while in School*

In the fall of 1929 this student was a non-reactor to tuberculin. She became a reactor in the spring of 1936. All films previously made of the chest were clear. In May 1936 a definite shadow appeared in the left second interspace. This slowly decreased and disappeared within approximately a year. We consider this lesion a primary focus. In the fall of 1938 she was employed as a resident physician in pediatrics.

In September 1929 as a freshman in the school of medicine this student was a non-reactor to tuberculin. He was found to be a reactor in August 1934. All roentgen-ray films prior to June 1934 were clear. During this month, however, there was evidence of disease at the level of the first interspace on the left side. Films in August 1935 revealed a decrease in the extent of the shadow. He was apparently well in 1938. We believe the lesion demonstrated by roentgen-ray film was only a part of a primary tuberculosis complex.

This student of medicine entered the freshman class in the fall of 1928 as a non-reactor to tuberculin. Roentgen-ray film of his chest in 1930 was clear. In June 1931, there was evidence of disease in the apex and first interspace of the right lung and in the first and second interspaces of the left lung. Films in February 1932, revealed no change in the shadows but in September 1934 and June 1935 the shadows had almost completely disappeared. He did not graduate until 1934. Since that time he has led an active life and is now practicing medicine. Apparently the lesions demonstrated by roentgen-ray film were only primary foci.

In the fall of 1930, this pre-medical student was a non-reactor to tuberculin. In February 1935 he was found to be a reactor. The same month an area of disease was revealed by roentgen-ray film at the level of the right third interspace near the periphery. In May 1935 the shadow had slightly increased in extent. In June it had decreased. In October and November 1935 and in January 1936 it remained unchanged. Later he had an interpretation of a small cavity by a roentgen-ray worker in another state. Artificial pneumothorax was instituted and he is still on that treatment. At no time have there been symptoms. In reviewing the case there is considerable doubt in our minds whether a significant cavity actually existed; or, if so, whether it represented anything more than a small cavity which one occasionally sees in a primary focus after the caseous center is eliminated through the bronchial tree. Usually these are of no clinical significance and disappear rather promptly as far as one can determine from roentgen-ray examination. Therefore, we are of the opinion that the lesion demonstrable by roentgen-ray film was a primary focus.

In the fall of 1929 as a freshman in the school of medicine, this student was a non-reactor to tuberculin. In February 1933 he was found to be a reactor. All films were clear until that time, when a small but definite area of disease was present at the level of the right fourth interspace. We consider this lesion as a primary focus. In October 1933 while serving as an intern, fluid accumulated in the right pleural cavity. This we regard as a reinfection form of tuberculosis dependent for its development on allergy and bacilli from a primary complex. In November 1934, there was definite evidence of a reinfection type of lesion in the apex of the right lung. In

January 1935 pulmonary hemorrhage occurred and tubercle bacilli were present in the sputum. Temporary interruption of the phrenic nerve has since been performed three times and he spent more than one year in bed. At present the shadow in the right apex has practically disappeared and he is practicing his profession.

In February 1930 as a freshman in the medical school, this student was a non-reactor to tuberculin. In February 1931 he reacted to the tuberculin test. Roentgen-ray films were clear. In May 1931, fluid was present in the right pleural cavity and a small area of disease was seen at the level of the third interspace in the right lung which we interpreted as representing the primary focus. After three months in bed, the fluid had disappeared. The shadow in the right third interspace remained unchanged through April 1933. He is now practicing medicine.

In February 1930 as a freshman in the school of medicine, this student was a non-reactor to tuberculin. Periodic tests revealed no reaction until after a tuberculosis service in the fall of 1932. In February 1933, effusion was present in the right pleural cavity. This had completely disappeared by June 1933. In August 1933, a small shadow was detected at the level of the right second interspace. This was still present and unchanged in June 1937 and August 1938. We have regarded this lesion as a primary focus. At present she is practicing her profession.

In March 1933 as a sophomore in the school of medicine, this student was a non-reactor to tuberculin. Periodic tuberculin tests resulted in no reaction until May 1935 when he was found to have fluid in the left pleural cavity. There was no evidence of effusion in August 1935. Roentgen-ray films of the chest have since been clear except for evidence of slight thickening of the pleura on the left side. The last examination was in April 1938. He is now practicing his profession.

In the spring of 1930, this pre-medical student was a non-reactor to tuberculin. Periodic tuberculin tests revealed no reaction until June 1933. All roentgen-ray films of the chest were clear until December 1934 when he had an effusion in the right pleural cavity. After several months the fluid disappeared. There is now no evidence of disease revealed by roentgen-ray film. He is practicing his profession.

In the fall of 1930, this pre-medical student was a non-reactor to tuberculin. In April 1933, he was found to be a reactor. In the summer of 1933 and the winter of 1934 films of the chest were clear. In February 1935, there was definite evidence of disease in the right subclavicular region. Periodic films over the next several months revealed no change. In October 1936, while serving as an intern there was possible roentgen-ray evidence of a small cavity in the area of disease. Because of the duration of time between the tuberculin reaction and the appearance of shadow we are of the opinion that this lesion represents the reinfection form of tuberculosis. Artificial pneumothorax was instituted and strict bed rest was employed for six months. There were no symptoms at any time. He is now working on a full-time basis.

As a freshman in the school of medicine in January 1932, this student was a non-reactor to tuberculin. Periodic tests revealed no reaction until February 1935. During the previous month he had spent two weeks on a tuberculosis service. Six weeks after leaving the service he developed fever and malaise. After having a fever of 102° to 104° for three weeks, erythema nodosum appeared. In November 1935, while he was an intern he developed pain over the right third costo-chondral junction, followed by a tumor mass in this region. Aspirated pus inoculated into guinea pigs resulted in tuberculosis. Two and one-half months later, he had curettement of the tuberculous chondritis. In March 1936, he experienced pain in the lumbar region. Roentgen-ray film of the lumbar spine revealed no evidence of disease. In July 1936, he complained of night sweats and fatigue. Examination revealed evidence of a left psoas abscess which was aspirated. He entered a sanatorium where the psoas abscess was aspirated several times. In January 1937, an abscess developed over the crest of the right ileum which drained spontaneously both posteriorly and laterally. In Decem-

ber 1938, there was still a small amount of drainage from the sinuses in the left inguinal region, the right iliac crest, and the right fifth lumbar region. At no time has there been any evidence of pulmonary tuberculosis. He resumed his internship in the fall of 1938.

B. *Those Who Had New Lesions Demonstrated after Graduation*

In 1930, this pre-medical student was a non-reactor to tuberculin. Periodic tests revealed no reaction until January 1933. All roentgen-ray films of the chest were clear through March 1935. In July 1935, pleural effusion was present on the left side. In November 1935, the fluid had completely disappeared. He is now apparently in good health and is practicing medicine.

In the spring of 1932, as a freshman in the school of medicine, this student was a non-reactor to tuberculin. Periodic tests revealed no reaction until November 1934. All roentgen-ray films through March 1935 were clear. In July 1935, he had a pulmonary hemorrhage while serving his internship. Roentgen-ray films revealed definite evidence of disease in the medial portion of the right upper lobe. Strict bed rest and artificial pneumothorax were instituted. He has continued on artificial pneumothorax and is now working full time as a physician.

In 1931 this pre-medical student was a non-reactor to tuberculin. Periodic tests revealed no reaction until December 1934. All roentgen-ray films of the chest throughout his medical course were clear. While practicing medicine in the spring of 1938, he was found to have pulmonary tuberculosis with cavitation involving the right lung. Tubercle bacilli were recovered from the sputum. Artificial pneumothorax was instituted and has been continued. He is now working on a part-time basis.

Thus, of 145 students who developed primary tuberculosis complexes under our observation, we know of 14 (9.6 per cent) who have had the location of the lesions demonstrated (tables 4 and 5). Attention must be

TABLE V

School of Medicine

145 developed primary complexes in school
- 14 (9.6 per cent) location of lesions detected
  - 4 (2.75 per cent) primary foci only
  - 5 (3.44 per cent) pleurisy with effusion only
  - 1 (0.69 per cent) extrapulmonary lesions
  - 4 (2.75 per cent) clinical pulmonary lesions

School of Education

686 reactors
- 3 (0.44 per cent) location of lesions detected
  - 1 (0.15 per cent) primary focus only
  - 2 (0.29 per cent) clinical lesions

called to the fact, however, that four (2.75 per cent) had evidence only of primary foci located by roentgen-ray film; five (3.44 per cent) had only pleurisy with effusion; one (0.69 per cent) developed extrapulmonary clinical tuberculosis; and four (2.75 per cent) developed clinical pulmonary disease. The remaining 131 would not have known of the presence of tuberculosis in their bodies had it not been for the routine periodic tuberculin test. In the entire group of 145, there has not been a case of meningitis, miliary disease, or tuberculous pneumonia.

In this study we have omitted a few questionable parenchymal lesions as we see no justification to include anything so indefinite as questionable

roentgen-ray findings. Moreover, we have omitted those with evidence of enlargement of the hilum shadows, since these are by no means always diagnostic tuberculous lesions.

Among the 45 students who replied to our questionnaire and stated that they had become tuberculin reactors since graduation, the following have shown evidence of lesions by roentgen-ray film examination:

As a freshman in the school of medicine in the fall of 1929 this student was a non-reactor to tuberculin. Periodic tests revealed no reaction throughout his medical course. Roentgen-ray films of the chest were clear. In 1935 while serving as an intern he was found to be a reactor. Roentgen-ray films of his chest revealed evidence of a lesion which proved to be due to a primary focus. This resolved so films of his chest were clear in 1937.

In the fall of 1929 this pre-medical student was a non-reactor to tuberculin. Periodic tests revealed no reaction throughout his course in medicine. All roentgen-ray films of his chest were clear. He became a reactor as an intern in 1934. In 1935 a shadow appeared in one lung which was interpreted as representing a primary focus. This had completely disappeared in 1938.

As a freshman in the school of medicine in the fall of 1930, this student was a non-reactor to tuberculin. Periodic tuberculin tests throughout his medical school course revealed no reaction. Roentgen-ray films of his chest were clear while in school. He became a reactor during the intern year. In February 1935 a lesion was detected at the level of the left second interspace. This was present through July 1935. In June 1938 the shadow could not be visualized on the roentgen-ray film.

As a freshman in the school of medicine in the fall of 1931, this student was a non-reactor to tuberculin. Periodic tests throughout his entire course in medicine revealed no reaction. Roentgen-ray films were clear. As an intern in 1934 he became a reactor. Roentgen-ray film examination revealed a shadow which was interpreted as representing a primary focus. The shadow later completely disappeared.

In the fall of 1931 as a freshman in the medical school this student was a non-reactor to tuberculin. All periodic tuberculin tests while in school revealed no reaction. Roentgen-ray films were clear throughout his medical school course. In 1935 (does not remember exact date) he was found to be a reactor to tuberculin. In the fall of 1935 while serving as an intern, a shadow appeared in the apex of the right lung. He was institutionalized for five months. No symptoms have been present at any time. Apparently the shadow represented a primary tuberculous focus.

Thus among 305 students of medicine who were tuberculin reactors when they entered the school of medicine or became reactors while in school, 18 (5.9 per cent) developed lesions which were located by roentgen-ray or other methods of examination (tables 4 and 5). Among the students in the College of Education on the campus of the University of Minnesota from 1932 to 1937, a total of 686 who reacted to tuberculin either on entrance to the college or subsequently had roentgen-ray film examination both on admission and just prior to graduation. Three (0.44 per cent) of these students developed lesions which were located by roentgen-ray film examination (tables 4 and 5). Neither in the School of Medicine nor the College of Education do we know of any who developed tuberculosis in the absence of a tuberculin reaction.

The findings of this study emphasize, in addition to the hazards of exposure, the fact that the entire span of life must be considered in every case

of tuberculosis whether the diagnosis is made by the tuberculin test alone or in addition the demonstration of the actual location of lesions. In contrast with most diseases dealt with daily by the physician the immediate results may be negligible, but the remote results, as in syphilis, may be disastrous.

In these students, we have seen the evolution of tuberculosis: the history of exposure, the first tuberculin reaction, occasional location by roentgen-ray of the primary focus, the reinfection type of lesions in the lungs, pleura, etc. Likewise, the procedures carried out in Group II represent our future course in tuberculosis control since records of tuberculin reactions should be available for the present generation of school children when a question of type of lesion arises.

Summary

1. In this study we have attempted to determine the tuberculosis situation among 1,441 persons who were in the University of Minnesota School of Medicine classes graduating from 1919 to 1932 inclusive (Group I). Thirty-one have died from non-tuberculous conditions. Of the remainder, 92.5 per cent replied to our questionnaire or evidence of death from tuberculosis was obtained. In this group 7.1 per cent reported having had clinical tuberculosis including pleurisy with effusion, while in school or since graduation. This represents 92 individuals or approximately the number of one entire class. Eleven have died from tuberculosis.

2. Two hundred forty-two physicians reported having had serious non-tuberculous illnesses from 68 disease entities. The first three causes of these illnesses in order of numbers were pneumonia, appendicitis, and scarlet fever.

3. We have attempted to determine also the tuberculosis situation among the members of four classes entering the school of medicine from 1929 to 1932 and graduating from 1933 to 1936 inclusive (Group II). These four classes include a total of 453 students, four of whom have died from non-tuberculous conditions. These students were studied by means of routine and periodic tuberculin tests, roentgen-ray films of the chest, and other indicated phases of complete examinations. Questionnaires were sent to all of the living graduates of these classes.

4. In Group I, 42 deaths have occurred, 11 of which were from tuberculosis. In Group II, there were four deaths, none of which was from tuberculosis. Hence, in the total group of 1,894 graduates from the Medical School from 1919 to 1936, there have been 46 deaths, 23.9 per cent of which have been due to tuberculosis.

5. On entrance to the School of Medicine, 35.6 per cent of the members of the four classes in Group II were reactors to tuberculin. On graduation, the proportion had increased to 68 per cent. Sixty-five who graduated as non-reactors to tuberculin have had subsequent tuberculin tests. Of these,

46.2 per cent had become reactors as interns and 31.1 per cent following internships. We now know of 78 per cent of the graduates of these four classes who are reactors to tuberculin.

6. In the College of Education of the University of Minnesota, 24.8 per cent of one class of students reacted to tuberculin on entrance and only 28.5 per cent of these same students reacted on graduation.

7. Among 160 students who already had primary tuberculosis complexes on entrance to the School of Medicine, two developed clinical tuberculosis while in school and three after graduation.

8. Of the 145 students who developed the primary tuberculosis complex while in school, 11 developed demonstrable lesions as students and three after graduation. Of these 14 students, four had only primary foci demonstrated by roentgen-ray film; one had clinical extrapulmonary tuberculosis; five had pleurisy with effusion; and four had chronic clinical pulmonary disease.

9. Of the students who developed primary complexes after graduation, as manifested by the tuberculin reaction, we know of five who had lesions in such locations as to be visualized by roentgen-ray film examination. All of these apparently were primary foci.

10. Among the students in Group II we have not learned of a case of tuberculous meningitis, miliary tuberculosis or so-called "infantile" tuberculosis.

11. In this entire study we know of no student with tuberculosis who did not react to the tuberculin test.

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THE INTRAVENOUS USE OF SODIUM SULFAPYRIDINE IN THE TREATMENT OF LOBAR PNEUMONIA *

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The intravenous use of sodium sulfapyridine was reported first by Marshall and Long.[1] Since the beginning of this study other reports [2, 3] on the parenteral use of sodium sulfapyridine for special indications have appeared. In none of these reports has the drug been given routinely and repeatedly. Data obtained from the routine repeated intravenous infusion of sodium sulfapyridine should be valuable in establishing the indications for its use by this route.

Material and Procedure

This report presents our experience with the intravenous use of sodium sulfapyridine monohydrate in the treatment of 54 patients suffering with lobar pneumonia. The patients in this study were admitted to the Grady Memorial Hospital in Atlanta, Georgia, between December 15, 1939 and March 16, 1940.

Typing for pneumococci by the quellung reaction was attempted from sputum or a throat swab of every patient at the time of admission. In many cases we were unable to type the sputum even after several attempts. Blood for culture and for a complete blood count and a urine specimen was obtained before treatment was instituted. Blood counts and urinalyses were repeated daily early in the course of the illness. Serial roentgenograms of the chest were made in every case.

The diagnosis of lobar pneumonia was made from the history, physical findings, laboratory studies, serial roentgenograms and autopsy findings. The rather typical response to sulfapyridine was confirmatory evidence.

The routine dose of sodium sulfapyridine was 0.06 gram per kilogram of body weight. This amount of the drug was dissolved in 750 c.c. of physiological saline solution or 5 per cent dextrose solution. Saline was used when vomiting occurred; dextrose solution if there was no emesis. This dose of the drug was repeated every six hours until the temperature dropped to normal. Then the same amount was given every eight hours. After the temperature had remained normal for 48 hours, the same dose was injected every 12 hours. After a second 48 hour afebrile period the intravenous sodium sulfapyridine was discontinued and 1.0 or 0.5 gram of sulfa-

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From the Department of Medicine of Emory University School of Medicine, Atlanta, Ga.

Part of the sodium sulfapyridine was available through the courtesy of the Calco Chemical Co.

TABLE I

Case No.	Sex	Age	Type	Lobe	I. V. Sulfapyridine		Oral Sulfapyridine		Maximum blood level in mg. %	Anti-serum in 100,000 units	Day of Disease	Crisis in hrs. after start of drug	Day of discharge or death	Days of nausea and vomiting	
					Total Gm.	No. of Doses	Total Gm.	No. of Doses							
1	F	22	—	LL	63.0	21	83.0	105	33.3		13	36	30		
2	M	15	—	LL	63.0	18	15.0	43	57.4		3	48	16	2	
3	M	64	—	RU	104.0	26	28.0	24	16.6		4	L	25	1	
4	F	65	—	LL	63.0	21	8.0	8	8.7		2	24	19	2	Delirious
5	F	38	XIX	RU	35.0	10	40.5	60	8.0		4	24	18	8	
6	F	48	—	LL	21.0	6	34.0	34	12.9		3	24	30	1	Rash with drug fever, 9th day
7	M	36	—	LL	8.0	2	83.5	123	5.7		5	L	33	4	Effusion
8	M	18	I	LL	41.0	15	—	—	10.5	1.0	2	36	20		Hematuria
9	M	52	I	LU	66.5	19	23.5	47	8.0	2.0	4	48	21		WBC 2,000 on admission
10	M	17	VII	RU LL	73.0	24	17.0	34	19.0		2	36	16	2	
11	F	37	—	RU	52.5	21	33.5	66	10.8		9	48	37	2	
12	F	47	XIV	LU LL RL	85.0	34	5.0	10	20.0	2.0	4	L	50	2	Irrational on admission
13	F	36	I	LL	82.5	33	6.0	12	15.4		1	L	26		Rash- 14th day
14	M	13	V	LL	24.0	12	11.0	22	13.3		1	48	14	3	
15	M	34	VIII	LL	130.0	38	3.5	7	14.8	1.4	3	L	49	3	Empyema with thoracotomy; alcoholism with DTs
16	M	64	—	RL	80.5	23	19.0	38	15.4		4	L	40	7	Thrombosis
17	F	19	V	RU	20.0	10	—	—	15.4	2.0	2	36	12	2	Irrational
18	M	26	—	LL RL	97.5	26	77.5	94	16.0		1	L	50	1	Irrational on admission. Effusion, thrombosis, spread 11th day
19	M	65	III	LU	63.0	21	2.5	5	7.5		3	24	13		
20	M	38	I	RL	73.0	21	16.5	32	6.4		1	72	20	1	Thrombosis
21	M	56	III	RL	80.0	20	15.0	30	13.5		3	48	25		
22	F	24	IV	LL RL	51.0	17	15.0	30	11.8		6	36	13	3	
23	F	76	—	LL	42.5	17	20.5	41	22.2		4	48	19		Irrational on admission
24	M	39	—	RU	64.0	18	7.0	13	23.5		3	48	18	1	Thrombosis
25	M	33	I	LU LL	52.5	15	31.5	63	23.5		1	36	46		Empyema
26	F	18	—	LL	40.0	20	21.5	42	9.5		5	24	20		

TABLE I—*Continued*

Case No.	Sex	Age	Type	Lobe	I. V. Sulfapyridine		Oral Sulfapyridine		Maximum blood level in mg. %	Anti-serum in 100,000 units	Day of Disease	Crisis in hrs. after start of drug	Day of discharge or death	Days of nausea and vomiting	
					Total Gm.	No. of Doses	Total Gm.	No. of Doses							
27	M	39	I	RU	42.5	17	1.0	1	33.3		2	60	26	7	Encephalopathy, 7th day; NPN 120, 8th day
28	F	18	I	LL	40.0	16	32.0	62	16.6		4	36	22	1	Effusion; thrombosis
29	F	15	—	RU	40.0	20	9.0	18	13.3		2	24	12		
30	F	33	I	RU LL	50.0	20	18.0	36	13.3		4	48	20		
31	M	14	V	RL	50.0	20	20.0	40	11.1		1	L	15	1	Thrombosis
32	M	37	VII	RM	15.0	5	—	—	10.0	2.2	1	48	14		Hemolytic anemia
33	M	18	I	RM	70.0	20	15.5	31	11.1		3	72	16	7	Thrombosis
34	M	29	I	LL	54.0	18	18.5	37	14.3		1	60	42	4	Irrational on admission; effusion
35	M	17	II	RL	22.5	9	27.5	47	7.1		1	36	15		Thrombosis
36	F	24	—	RL	42.5	17	23.0	27	6.7		2	48	20		
37	F	13	—	RL	16.0	8	9.0	17	12.5		1	36	11		
38	F	13	I	LL	6.0	3	—	—	3.5	2.0	2	48	18	1	Hematuria
39	M	23	IV	LL	60.0	20	11.0	22	12.5		1	36	16	5	Delirious on admission NPN 46
40	M	17	I	RU	27.0	9	—	—	20.8	2.0	1	36	19	4	Delirious on admission; thrombosis; NPN 100
41	F	54	—	RU	10.0	4	—	—	10.4		2	36	20		Hematuria
42	M	44	I	LL	54.0	18	12.5	25	9.1		1	72	12		Thrombosis
43	M	23	V	RM	45.0	15	21.0	42	6.2		2	36	13	1	Thrombosis
44	M	40	—	RM RL	54.0	18	19.0	38	6.6		?	36	36		Spread, 6th day
45	F	59	—	RU	15.0	6	—	—	6.6		1	36	23	1	Hemoglobinuria
46	F	25		LL	12.5	5	3.0	3	5.8		2	L	23		Hematuria on admission
47	M	52	XX	LL	56.0	12	—	—	25.0	1.0	?	—	6	3	Convulsions
48	M	49	XIV	RL	49.0	13	—	—	16.6	3.0	2	—	5	1	Irrational; effusion, anuria
49	F	64	—	LL	44.0	22	12.0R	6R	20.0		4	—	9	2	
50	M	55	I	RL	38.5	11	3.0R	1R	13.3	3.0	3	—	4		Irrational on admission. Empyema, hematuria, bacteremia
51	M	73	III	RU RM	32.5	9	—	—	26.7		?	—	3	1	
52	M	59	III	LU LL	24.0	7	—	—	4.0	2.0	3	—	6		Effusion
53	M	84	—	LL	16.0	5	—	—	—		2	—	5		
54	F	76	—	RM RL	13.0	6	—	—	25.0		4	—	2		

pyridine was given by mouth every four hours. An equal amount of sodium bicarbonate was given by mouth with each dose of sodium sulfapyridine or sulfapyridine. If the patient's response seemed unsatisfactory 48 hours after the parenteral injection of the drug was begun, type specific anti-serum was administered.

Just before all but the initial injections of the drug venous blood was withdrawn for a determination * of the amount of free sulfapyridine present. By obtaining the specimen before each injection we determined

TABLE II

		Group		Survivors		Fatalities	
		Aver.	Range	Aver.	Range	Aver.	Range
Intravenous	Total Gm.	48	6–130	50	6–130	34	13–56
	No. Doses	16	2–38	17	2–38	11	5–22
Oral	Total Gm.	16	0–84	19	0–84	0	0
	No. Doses	26	0–123	31	0–123	0	0
Maximum blood sulfapyridine mg. %		14.7	3.5–57.4	14.1	3.5–57.4	18.7	4.0–26.7
No. Hosp. Days		21	2–50	23	11–50	5	2–9

TABLE III

Days elapsing between onset and admission			
1 day	14 cases	5 days	2 cases
2 days	13 cases	6 days	1 case
3 days	9 cases	7+ days	2 cases
4 days	10 cases	unknown	3 cases

the lowest concentration of the drug in the blood. It is reasonable to suppose that higher concentrations were present in all of these patients during and shortly after the infusions.

Table 1 presents a summary of pertinent data for each of the 54 cases in this series.

In table 2 are shown the amounts of the drug given intravenously and orally. The average of the highest determination of free sulfapyridine in the blood in each case is given; the range of these values is also indicated. The number of hospital days is also given in average and range.

* *Blood:* Three c.c. of oxalated whole blood were measured into a flask and laked with 24 c.c. of 0.05 per cent aqueous solution of saponin, shaken and allowed to stand for 2 minutes. Three c.c. of 20 per cent trichloracetic acid were added, shaken, and allowed to stand 1 minute, and then filtered. Ten c.c. of the filtrate were measured into a small flask and 1 c.c. of 0.1 per cent of freshly prepared sodium nitrate solution was added. This solution stood for 3 minutes and then there was added to it 5 c.c. of a solution of dimethyl-alpha-naphthalamine (1 c.c. of concentrated dimethyl-alpha-naphthalamine dissolved in 250 c.c. of 95 per cent ethyl alcohol). The resulting purplish-red azo dye was compared colorimetrically with a similarly treated standard.

Of the 54 patients studied 32 were males and 22 were females. The ages varied from 13 to 84 years. The average age of the whole group was 38 years; of the survivors 34 years; and of the fatalities 64 years. There were 22 patients aged less than 30 years; 23 between 30 and 59 years, and 9 patients aged 60 or more years. The number of days elapsing between the onset of the pneumonia and admission to the hospital is shown in table 3. The average elapsed time for the group was 2.84 days; for the survivors 2.82 days, and for the fatalities 3.0 days.

The incidence of the types of pneumococci in this series is shown in table 4. The lobe (or lobes) involved is shown in table 5.

TABLE IV

Type I	14 cases
Type II	1 case
Type III	4 cases
Type IV	2 cases
Type V	4 cases
Type VII	2 cases
Type VIII	1 case
Type XIV	2 cases
Type XIX	1 case
Type XX	1 case
Undetermined	22 cases

TABLE V

Lobe involved:		Combined:	
Left lower	20 cases	LL and LU	2 cases
Left upper	2 cases	LL and RU	2 cases
Right lower	9 cases	LL and RL	2 cases
Right upper	10 cases	LL, LU and RL	1 case
Right middle	3 cases	RM and RL	2 cases
Combined	10 cases	RM and RU	1 case
	54 cases		10 cases

RESPONSE

There were eight deaths (14.8 per cent mortality) in this group of 54 patients who were treated with sodium sulfapyridine intravenously.

Of the 54 patients, six (11.1 per cent) had a normal temperature within 24 hours after the drug was first administered. Sixteen (29.6 per cent) were afebrile within 36 hours; ten (18.5 per cent) within 48 hours; and five (9.3 per cent) within 72 hours. Of the 46 patients who recovered, nine (16.7 per cent of the 54) required longer than 72 hours to reach an afebrile state.

There was a spread of the pneumonic process in one fatal and two surviving cases. In the fatal case (number 47) the spread occurred after the drug had been discontinued because of tonic and clonic convulsions. The initial response of the infection was typical with crisis. Death was considered to be due to the toxic reaction from the drug.

The first surviving patient (number 1) had had an initial crisis within 36 hours and had been receiving 1.0 gram of sulfapyridine by mouth every four hours for six days. On the eleventh hospital day, while the free sulfapyridine in the blood was 3.3 mg. per cent, a spread of the pneumonia occurred. Sodium sulfapyridine was injected again but this time the response was by lysis.

The other surviving patient (number 18) was apparently well when the intravenous sodium sulfapyridine was stopped on the tenth hospital day. The free sulfapyridine content was 2.6 mg. per 100 c.c. of blood before the last injection. The oral administration of sulfapyridine was begun with 0.5 gram every four hours. The next day the blood level of free sulfapyridine was too low to read. The patient developed a pain over the contralateral lung, fever, and signs of consolidation. Sulfapyridine was increased to 1.0 gram every four hours and the patient recovered by lysis.

Administration of the drug was stopped on 11 surviving patients (numbers 6, 8, 13, 17, 27, 32, 38, 40, 41, 45, 46) because of hematuria, encephalopathy, rash or hemolytic anemia. Six of these recovered without further chemotherapy or specific anti-serum. The other five (numbers 8, 17, 32, 38, 40) were given type specific anti-serum the day the drug was stopped or the following day. While the drug was being continued, anti-serum was given to three patients (numbers 9, 12, 15); to one because of a very poor prognosis and to the other two because of leukopenia. The remaining four of the 12 patients who received anti-serum were in the fatal group.

Blood Cell Changes

The erythrocyte counts made on admission showed: more than 5 million erythrocytes in 6 cases; 4 to 5 million erythrocytes in 37 cases; 3 to 4 million erythrocytes in 10 cases; less than 3 million erythrocytes in 1 case.

During the course of the pneumonia, while frequent counts were being made, 15 cases showed a decrease of from 1 to 2 million erythrocytes per cu. mm. Five cases showed a decrease of more than 2 million below the admission count. Only one of these had acute hemolytic anemia. Transfusions of whole citrated blood were given to nine patients.

The leukocyte counts made on admission showed: more than 20,000 leukocytes in 23 cases; 10,000 to 20,000 leukocytes in 23 cases; 5,000 to 10,000 leukocytes in 6 cases; less than 5,000 leukocytes in 2 cases (2,000, 4,600).

Only two patients showed a subsequent decrease of leukocytes below 4,000 per cu. mm. Both had a low count of 3,900.

Only one positive blood culture (case number 50) was obtained.

Blood Levels

At the outset it was hoped that there would be some constancy in the free sulfapyridine levels in the blood. The variation of blood levels, how-

ever, with intravenous sodium sulfapyridine seemed almost as great as with oral sulfapyridine. In chart 1 is shown the great spread of the values for free sulfapyridine in the blood. All of these values were obtained while the

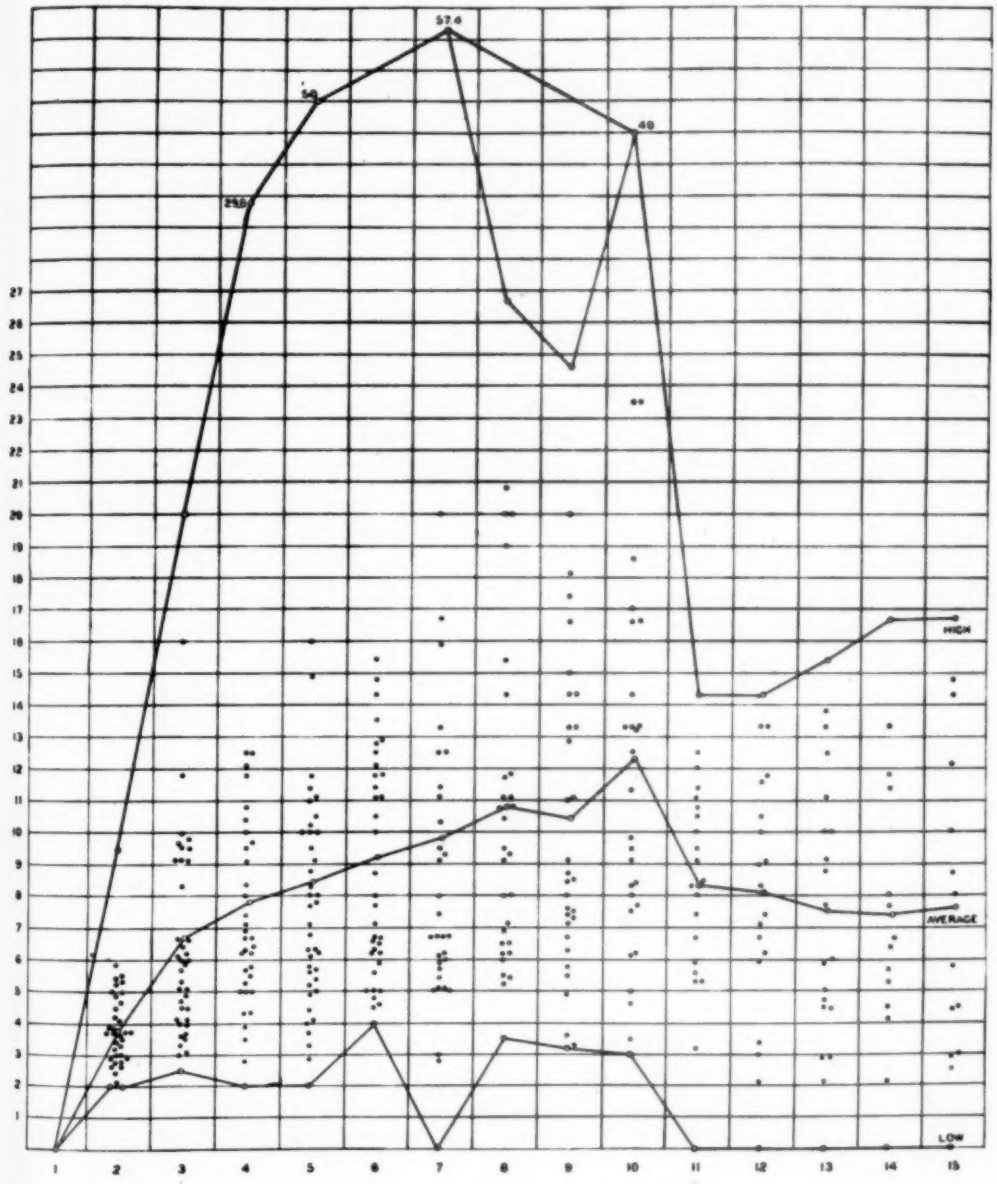

CHART 1. Levels of free sulfapyridine in the blood observed during the course of repeated intravenous injections of sodium sulfapyridine monohydrate.

patients were receiving the routine dose of sodium sulfapyridine every six or eight hours intravenously. The negative determination before the seventh injection was the last one in case number 52 which terminated fatally soon thereafter. The negative determinations which were obtained before the eleventh, twelfth, thirteenth, fourteenth and fifteenth infusions were all from the same case (number 36) which recovered without complications. The four readings above 27 mg. per cent on chart 1 occurred in the second patient treated. This patient, while receiving a 2 per cent solution of the drug, had marked nausea and vomiting which resulted in dehydration and the extremely high blood concentration. Following this experience, the drug was dissolved in 750 c.c. of saline or dextrose so that a patient getting an injection every six hours would have a daily fluid intake of at least 3000 c.c. Two surviving patients (numbers 1 and 27) had high blood levels of 33.3 mg. per cent after taking the drug orally (not shown on chart 1). Five patients (numbers 24, 25, 40, 51, 54) on chart 1 and four patients (numbers 12, 23, 47, 49) not on chart 1, had high concentrations between 20 and 30 mg. per cent. Of these nine, four were in the fatal group. We, as others,[3, 4, 5] are impressed with the fact that high blood levels of free sulfapyridine seem no more effective than those of 3.0 to 4.0 mg. per cent.

The most marked variation in blood levels existed between different individuals. In the same person, however, there was often a rather marked variation while the same amount of drug was being injected at a regular interval. In chart 1 the curve representing the average level before each injection rises through the tenth injection. The subsequent fall would be expected, for by then most of the patients were receiving their injections every eight hours instead of every six hours.

In chart 1 is indicated the wide range in the blood level of free sulfapyridine that may be expected when a standard dose is administered intravenously. The data collected in this study are not sufficient to explain this variation. We regret that total as well as free sulfapyridine levels were not determined. As a result, we are unable to say how important a part is played by the rate at which sulfapyridine is acetylated. The charting of the fluid intake and output was not of sufficient accuracy to justify its use in determining the influence of the speed of urinary excretion on the blood level of the drug. These data do suggest that, after ingestion of sulfapyridine, differences in the rate and degree of absorption from the alimentary tract do not play as important a part in the variation of blood levels of free sulfapyridine as was originally supposed.

There was no unusual elevation of free sulfapyridine in the blood of six patients who developed hematuria:

Case 8 received 33 gm. in 72 hours. The highest concentration reached was 10.5 mg. per cent.

Case 38 received 6 gm. in 24 hours with a high concentration of 3.5 mg. per cent.

Case 41 received 10 gm. in 24 hours with a high concentration of 10.4 mg. per cent.

Case 45 received 15 gm. in 36 hours with a high concentration of 6.6 mg. per cent.

Case 46 received 12.5 gm. in 36 hours with a high concentration of 5.8 mg. per cent.

Case 50 received 31 gm. in 60 hours with a high concentration of 13.3 mg. per cent.

Toxic Reactions to Drug

Nausea and vomiting occurred more frequently than any other toxic reaction. It was present in 31 cases, lasting from one to eight days with an average duration of 2.7 days. In no case was it severe enough to require stopping of the drug. The nausea and vomiting frequently began

Table VI

Case No.	High Blood Level	High Vomitus Level
16	13.3 mg. per cent	50.0 mg. per cent
33	11.1 mg. per cent	20.0 mg. per cent
39	8.0 mg. per cent	10.0 mg. per cent
18	16.0 mg. per cent	3.2 mg. per cent

Table VII

Reaction	No. Cases	Per Cent	Drug Stopped	Deaths
Nausea and vomiting	31	57.4	0	4
Encephalopathy	4	7.4	3	1
Rash	3	5.6	3	1
Hemolytic anemia	1	1.9	1	0
Granulopenia	0	0.0	0	0
Hematuria	6	11.1	6	1
Nitrogen retention	4	7.4	2	1
Anuria	1	1.9	0	1

about 15 minutes after the beginning of an injection, was most severe during the infusion and tended to subside following completion of the injection. With the first patients a 2 per cent solution was used. Nausea and vomiting were found to be more severe with the concentrated solution than with the drug dissolved in 750 c.c. of solution.

The vomitus of four patients was studied for its content of free sulfapyridine. In the vomitus of three of these, the concentration of free sulfapyridine was greater than the highest level determined in the blood during the same day as shown in table 6.

In table 7 are listed the toxic reactions that occurred in this series. Under encephalopathy are listed four cases in which delirium, irrationality, or convulsions developed after administration of the drug. There were seven other cases in which encephalopathy was present before treatment was instituted. One case of hemoglobinuria is listed as hematuria. Nitrogen

retention was shown by elevation of the non-protein nitrogen. In the four cases, the highest determination for each was 46, 100, 120 and 120 mg per cent. We were not concerned with cyanosis due to the drug.

Complications

Three patients developed empyema after treatment was started. One of these patients (number 52) died. One of the two survivors required thoracotomy. A pleural effusion developed in six other cases (11.1 per cent), including one fatal case. There were no cases of meningitis, endocarditis, otitis or phlebitis in this group of patients.

Taplin, Jacox and Howland [6] have reported the use of sodium sulfapyridine by hypodermoclysis in from 0.3 to 0.7 per cent solution in physiologic solution of sodium chloride without the observation of a single local reaction in any of the more than 50 patients treated by this route. In our series, however, we encountered, in 11 cases, antecubital thrombosis with surrounding soreness and induration associated with the intravenous infusion of 0.27 to 0.53 per cent solution of sodium sulfapyridine.

Mortality

In an unselected series of 54 cases of lobar pneumonia, not much importance may be attached to the mortality rate. However, since our rate of 14.8 per cent is higher than that reported as occurring in many series of lobar pneumonia treated with sulfapyridine we would like to summarize our fatal cases.

Case 47. A 52-year-old male had been a deaf and dumb moron since he had had meningitis at the age of three years. He was admitted with Type XX left lower lobar pneumonia of unknown duration. After two infusions of 4.8 grams of sodium sulfapyridine, he developed violent tonic and clonic convulsions. The temperature, pulse, and respirations were normal after the third infusion, but the convulsions continued with such severity that on the third day the drug was stopped after seven injections. The next day the temperature rose to 103.2 degrees. Type XX anti-serum, 100,000 units, was given. On the fifth day his clinical condition was so much worse that the drug was resumed. Five infusions of 4.5 grams were given. On the sixth day convulsions and pulmonary edema were terminal events.

Case 48. A 49-year-old male was admitted with Type XIV right lower lobar pneumonia of two days' duration. Temperature on admission was 106.0 degrees. Subsequently, the temperature varied between 101.4 and 107.0 degrees. The initial leukocyte count was 4,600. This gradually increased to 13,550 on the fifth day. During the second hospital day the patient became irrational. During the third day 300,000 units of Type XIV anti-serum were given. An effusion was present. Anuria developed during the fourth day and persisted until the patient died during the fifth day of hospitalization.

Case 49. A 64-year-old female was admitted four days after the onset of left lower lobar pneumonia of undetermined type. During the first six hospital days the temperature varied between 98.6 and 102.4 degrees. On the seventh day the temperature rose to 105.6 degrees. Peripheral circulatory failure developed and persisted until the patient died during the ninth hospital day. When failure developed,

the administration of the drug was changed from intravenous infusions to rectal instillations without benefit.

Case 50. A 55-year-old male was admitted with Type I right lower lobar pneumonia of three days' duration. He was irrational on admission. The blood culture was positive for Type I pneumococci. Thoracentesis on the second day yielded 300 c.c. of pus containing the same organism. During the second and third days 300,000 units of Type I anti-serum were given. Hematuria developed during the third day shortly before the patient died 76 hours after admission.

Case 51. A 73-year-old male was admitted with Type III right upper and middle lobar pneumonia of unknown duration. This patient had attended the out-patient clinic since 1932 with angina pectoris. In 1937, he was admitted for treatment of coronary artery disease. Generalized arteriosclerosis was pronounced. On the second hospital day the blood non-protein nitrogen was 120 mg. per cent. During the same day peripheral circulatory failure developed and persisted until the patient died on the third day.

Case 52. A 59-year-old male was admitted three days after the onset of Type III left upper and lower lobar pneumonia with effusion. On the second hospital day a maculopapular rash developed over the abdomen, shoulders, wrists and knees after two infusions of sodium sulfapyridine had been given. The drug was stopped, but the rash increased. During the same day 200,000 units of Type III anti-serum were given. During the fifth day a thoracentesis yielded 350 c.c. of cloudy fluid containing Type III pneumococci. Because of the seriousness of the patient's condition, sodium sulfapyridine infusions were resumed and 100,000 additional units of anti-serum were given, but the patient died during the sixth hospital day.

Case 53. An 84-year-old male was readmitted after being at home for 10 days following hospitalization of a month for senility and emaciation. A roentgenogram revealed left lower lobar pneumonia, but the clinical findings were not compatible with lobar pneumonia until the fourth day when the temperature rose to 103.2 degrees. Sodium sulfapyridine was begun then but the patient died the next day. Autopsy revealed: left lower lobar pneumonia, pulmonary tuberculosis with a cavity four centimeters in diameter in the right upper lobe, bilateral fibrous pleurisy, generalized arteriosclerosis with calcification of the larger vessels, concentric myocardial hypertrophy, granular contracted kidneys, chronic cholecystitis with cholelithiasis and hydrops of the gall-bladder, emaciation and decubitus ulcers.

Case 54. A 76-year-old female, senile and emaciated, was admitted with right middle and lower lobar pneumonia of four days' duration. On admission her temperature was 99.6 degrees. It did not rise above 100.6 degrees. Before the sixth infusion of sodium sulfapyridine the blood level of free sulfapyridine was 25 mg. per cent. This infusion of 2.0 grams in 750 c.c. of 5 per cent dextrose in physiological saline was given in one hour. The patient died 10 minutes after the completion of the infusion and 32 hours after admission.

Conclusions

1. The intravenous administration of a solution of sodium sulfapyridine monohydrate is a safe procedure.

2. Sodium sulfapyridine should be used intravenously only when there is a special indication.

3. The concentration of free sulfapyridine in the blood after intravenous administration is usually higher than after oral ingestion but:

(*a*) Unusually high concentrations seem no more effective than those of 3 to 4 mg. per cent.

(*b*) There is no added constancy of the blood level of free sulfapyridine after intravenous administration.

(*c*) The mortality rate of 14.8 per cent after the routine administration of sodium sulfapyridine intravenously is not lower than the reported mortality rate after oral administration of sulfapyridine.

(*d*) Complications of lobar pneumonia are not prevented by the intravenous injection of sodium sulfapyridine.

(*e*) Toxic reactions in this series are of about the same or of slightly greater frequency than in reported groups receiving the drug orally.

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PHONOCARDIOGRAPHY AND ITS CLINICAL CORRELATION *

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Ever since the discovery of the heart sounds by Harvey in 1626, there must have been a desire for their graphic representation on the printed page. For, according to Orías and Braun-Menéndez [1] the skeptics of that day denied the existence of the heart sounds even after Harvey's classical description of the same. The refusal to recognize Harvey's discovery went so far as for one authority to state that such perfect auditory acuity as to hear heart sounds could exist only in London and nowhere else in the world. Visual demonstration would certainly have helped then to convince doubters of facts, as it frequently does even now.

The necessity for graphic recording of heart sounds must have arisen again almost two centuries later when Laennec defined and interpreted heart murmurs. It must have been urgent again to invoke the visual sense as an aid to the auditory sense, in order to locate the precise position of the murmur in the heart cycle. And, even today, the necessity for such help from the visual sense organ is still apparent.

Since then many attempts at graphic representation of the heart sounds and heart murmurs have been made. But it was not until the close of the 19th century that real progress had been made and that was with the introduction of Einthoven's method of electrophonic amplification and recording.[2] Subsequently various devices have been introduced, the most popular ones being the electrical or indirect method and the capsular [3] or direct method of recording heart sounds and murmurs.

The normal heart sounds as well as the various murmurs have already been studied and recorded by many investigators and have been clearly defined as to duration of each sound, number of vibrations for each sound and murmur.[1, 4, 5, 6] This paper deals with the clinical correlation of phonocardiography and organic heart disease.

Procedure

Two hundred cases of the most common varieties of organic heart disease were studied graphically and clinically. The heart sounds were recorded simultaneously with the electrocardiogram on the Cambridge electrocardio-stethograph.[7] The number of patients included 190 adults and 10 children. The adults varied in age from 18 to 76 and included only 14 females. The 200 patients included 181 definitely diagnosed cases of or-

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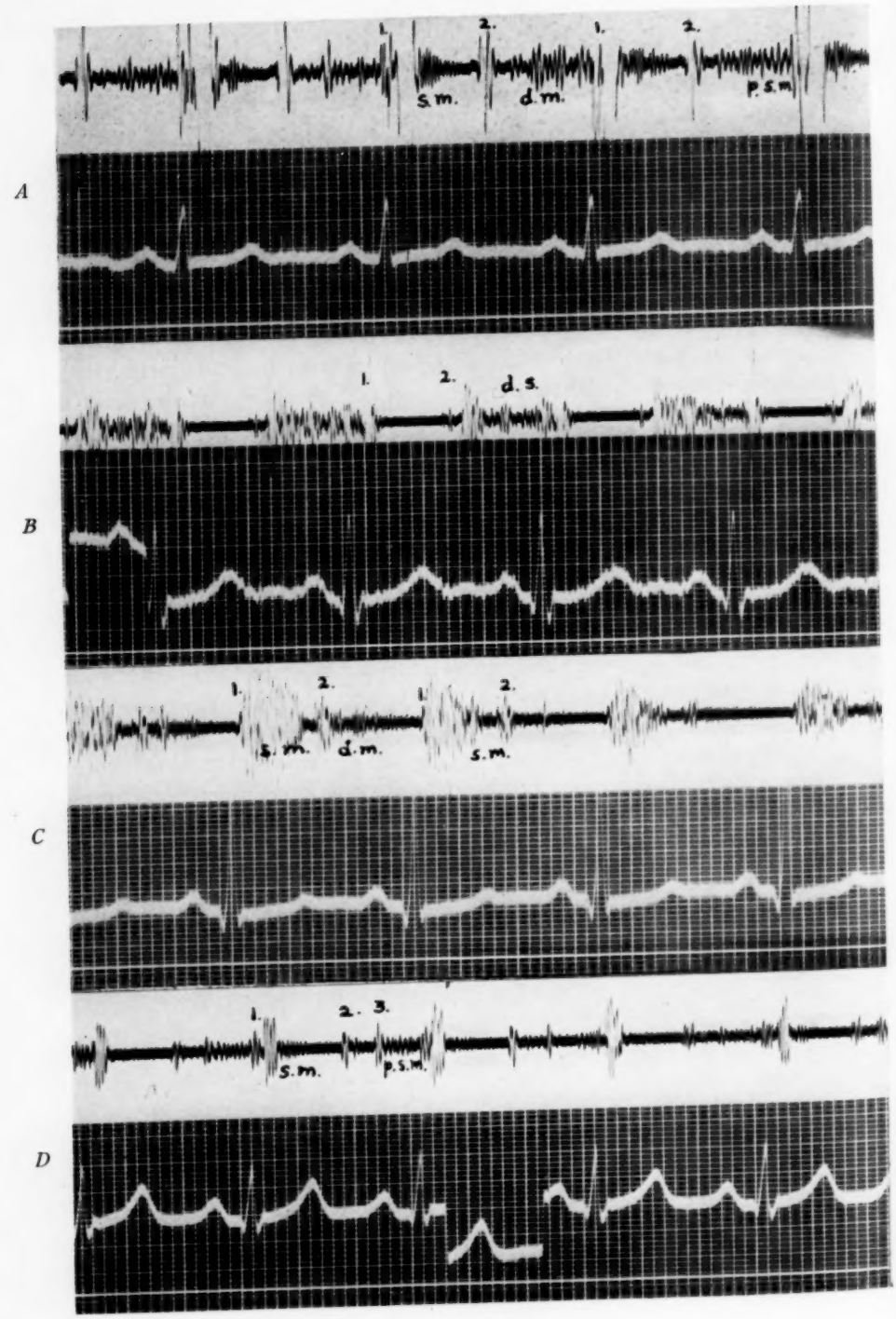
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ganic heart disease in various stages of functional capacity; 9 were unclassified and 10 were considered possible or potential heart disease.

In order to evaluate the efficiency of the recording instrument as compared with the clinical findings, all heart sounds, murmurs, and gallop sounds were recorded separately, after each examination. The graphic record of the patient, made soon after the examination and with the individual in the same position, was interpreted independently and recorded in parallel column on the patient's chart. The criteria of Wiggers,[4] Boyer, Eckstein and Wiggers [5] and of Orías and Braun-Menéndez,[1] were used for determining what constitutes a normal heart sound and what constitutes a murmur. Thus the first sound recorded from the apex consists of 5 to 11 vibrations and extends over a period of 0.06 to 0.11 second. The second sound consists of 3 to 4 vibrations and extends over a period of 0.04 to 0.06 second. The third sound consists of 1 to 3 vibrations and takes place 0.11 to 0.14

TABLE I

Two Hundred Patients Studied
Diagnosis

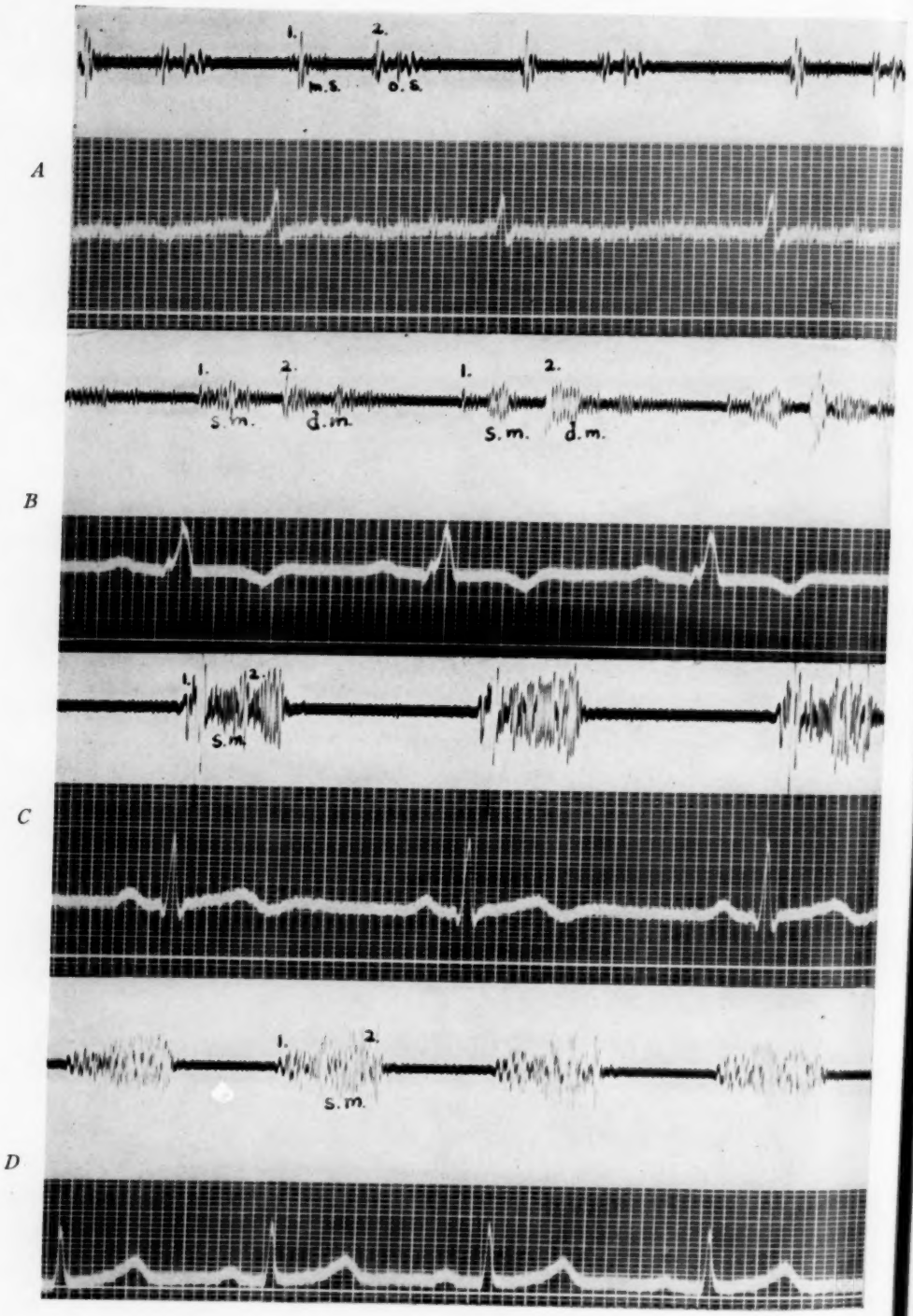
	Rheumatic	Hypertensive	Syphilitic	Coronary	Congenital	Undetermined	Potential and Possible	Total
No. of Patients	70	44	35	26	6	9	10	200

second after the beginning of the second sound. And the fourth or auricular sound begins 0.04 second after the origin of the P-wave in the electrocardiogram and consists of 2 to 5 vibrations. The cycles denoting the murmurs following the normal sound or replacing the sound are usually indistinguishable from the vibrations of the normal sound. It is the number of vibrations and the time factor above the maximum number of cycles encountered in normal sounds that determine the murmur. Systolic murmurs including the sound may have 13 to 35 vibrations or even more and may extend over a time period to reach or pass the second sound: or, it may be so short as to extend over a period not longer than 0.02 to 0.03 second past the first sound.

The diastolic murmur together with the second sound consist of 7 to 45 vibrations. It may be so short as to extend over a period of 0.07 second, or over the entire diastole and even continue with a late diastolic or presystolic murmur to merge with the succeeding first sound.

FIG. 1. *A*. Rheumatic heart disease, mitral stenosis and insufficiency with late diastolic or presystolic murmur. *B*. Rheumatic heart, mitral stenosis and insufficiency with aortic insufficiency. *C*. Rheumatic aortic insufficiency and stenosis, with mitral insufficiency. *D*. Rheumatic heart disease with physiological third sound.

S.M.—Systolic murmur
D.M.—Diastolic murmur
P.S.M.—Presystolic murmur.


1.
2.
m.s.
o.s.
A
1.
2.
s.m.
d.m.
1.
2.
s.m.
d.m.
B
1.
2.
s.m.
C
1.
2.
s.m.
D

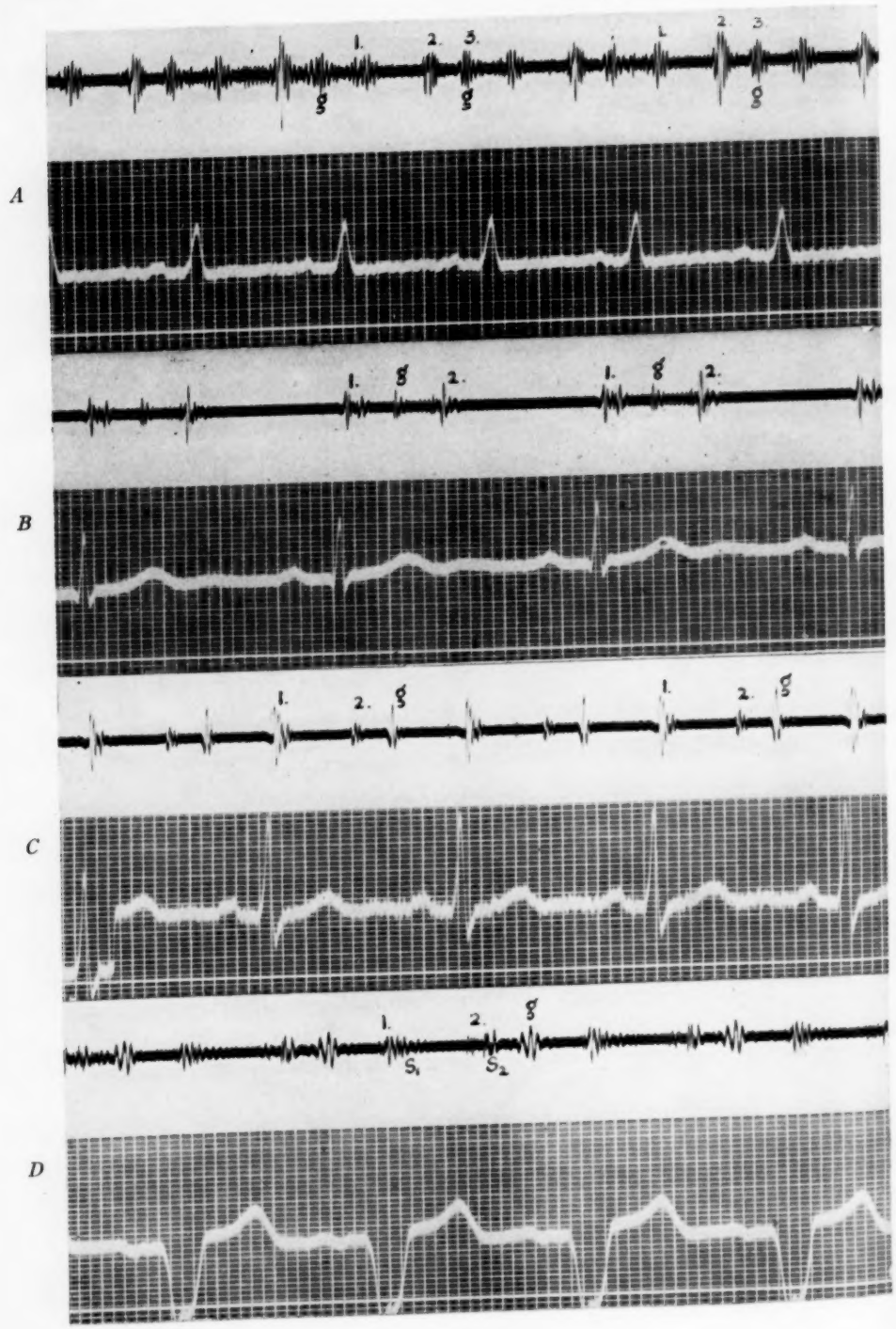
Based on the above criteria there was a remarkable uniformity and agreement between the clinical description of the murmurs and the graphic interpretation of the same. However, in about 10 per cent of the diastolic murmurs of aortic insufficiency the interpreted graphic record did not correspond with the clinical record. That is, the murmur was definitely heard on physical examination and through the stethophone but was not represented by vibrations on the phonocardiogram. If the amplification was increased, many adventitious vibrations appeared and distorted the base line or silent period between sounds. On the other hand, late diastolic murmurs or presystolic murmurs of mitral stenosis were occasionally recorded graphically but were not described clinically, only to be confirmed on subsequent reexaminations. Systolic murmurs were almost always recorded graphically when they were described clinically. At no time, however, was a systolic murmur recorded graphically when it was not heard on physical examination but it was not recorded in eight instances where it was repeatedly heard on examination. It was, however, only in the distantly heard murmurs of low intensity that the instrument failed to record them or did so poorly.

Thus out of 168 clinically recorded systolic murmurs among the 200 patients studied, 160 were recorded graphically. Out of the 75 clinically recorded diastolic murmurs, only 67 were recorded graphically. But late diastolic murmurs were recorded graphically in five instances more than it was described clinically.

The Third and Fourth Sounds

It is in the phase of the cardiac cycle when extra sounds are frequently encountered that the recording instruments serve mostly. Both the third as well as the fourth sounds are often missed on physical examination, and when either one of these is described clinically it is not always placed in its exact position in the cardiac cycle. Such differentiation, that is whether the additional sound heard on examination is a third sound following the second, or is a fourth or auricular sound may not be of much clinical significance but it indicates the advantage of graphic recording over the ear, for on the phonocardiogram it is at once definitely recorded and in its exact sequence. Moreover, in cases of doubt with reference to clinical gallop it is important to definitely and precisely locate the extra sound; whether it is in mid-systole which is interpreted as systolic gallop or mid-systolic click[8]; whether it occurs soon after the second sound and, therefore, falls in the category of the opening snap of mitral stenosis, or whether it is a third sound, protodiastolic gallop, or an accentuated auricular sound, or presystolic gallop.

Fig. 2. *A.* Rheumatic heart disease with auricular fibrillation and opening snap of mitral stenosis. Vibrations of murmurs barely visible because of diminished amplification to visualize the third sound (O.S.—opening snap). *B.* Syphilitic aortic insufficiency with aneurysm. *C.* Sclerotic aorta with aneurysm. *D.* Congenital patent ductus.


A
B
C
D
1.
2.
3.
g
S_1
S_2

Extra sounds were recognized clinically in 48 instances. They were described as a third sound in 42 patients and as a fourth sound in six patients. But they were graphically recorded 21 times as a fourth sound and 37 times as a third sound, indicating gross errors in timing and locating the extra sound with reference to its exact position in the cardiac cycle and also failure in recognizing it altogether in over 15 per cent of the individuals in whom extra sounds were present.

Of the 37 graphically recorded third heart sounds, 17 were described clinically as the opening snap in mitral stenosis, 11 as protodiastolic gallop and nine were classed as physiological third heart sounds. Of the 21 graphically recorded fourth heart sound, ten were clinically considered presystolic gallop, three as presystolic and protodiastolic gallop coexisting, and

TABLE II

Comparative Graphic and Clinical Record of Murmurs, Third and Fourth Heart Sounds

Organic Heart Disease	No. of Cases	Murmurs				Third Sound		Fourth Sound	
		Graphic		Clinical					
		Systolic	Diastolic	Systolic	Diastolic	Graphic	Clinical	Graphic	Clinical
Rheumatic	70	66	52	68	50	15	14	7	3
Hypertensive	44	26	—	27	1	9	13	8	3
Syphilitic	35	24	20	27	23	4	3	—	
Coronary	26	23	—	23	1	4	6	3	
Congenital	6	6	—	6	—	—	3	2	
Possible and Potential	10	8	—	8	—	2	3	2	
Undetermined	9	9	—	9	—	3	3	3	—
TOTAL	200	162	72	168	75	37	42	21	6

eight were considered auricular sounds in cases of flutter, congenital heart disease, nodal rhythm, A. V. block, and in two patients of active rheumatic carditis, and in two others classified as possible or potential heart disease, one of whom had a thoracoplasty in the cardiac area, allowing the auricular sound to be distinctly audible.

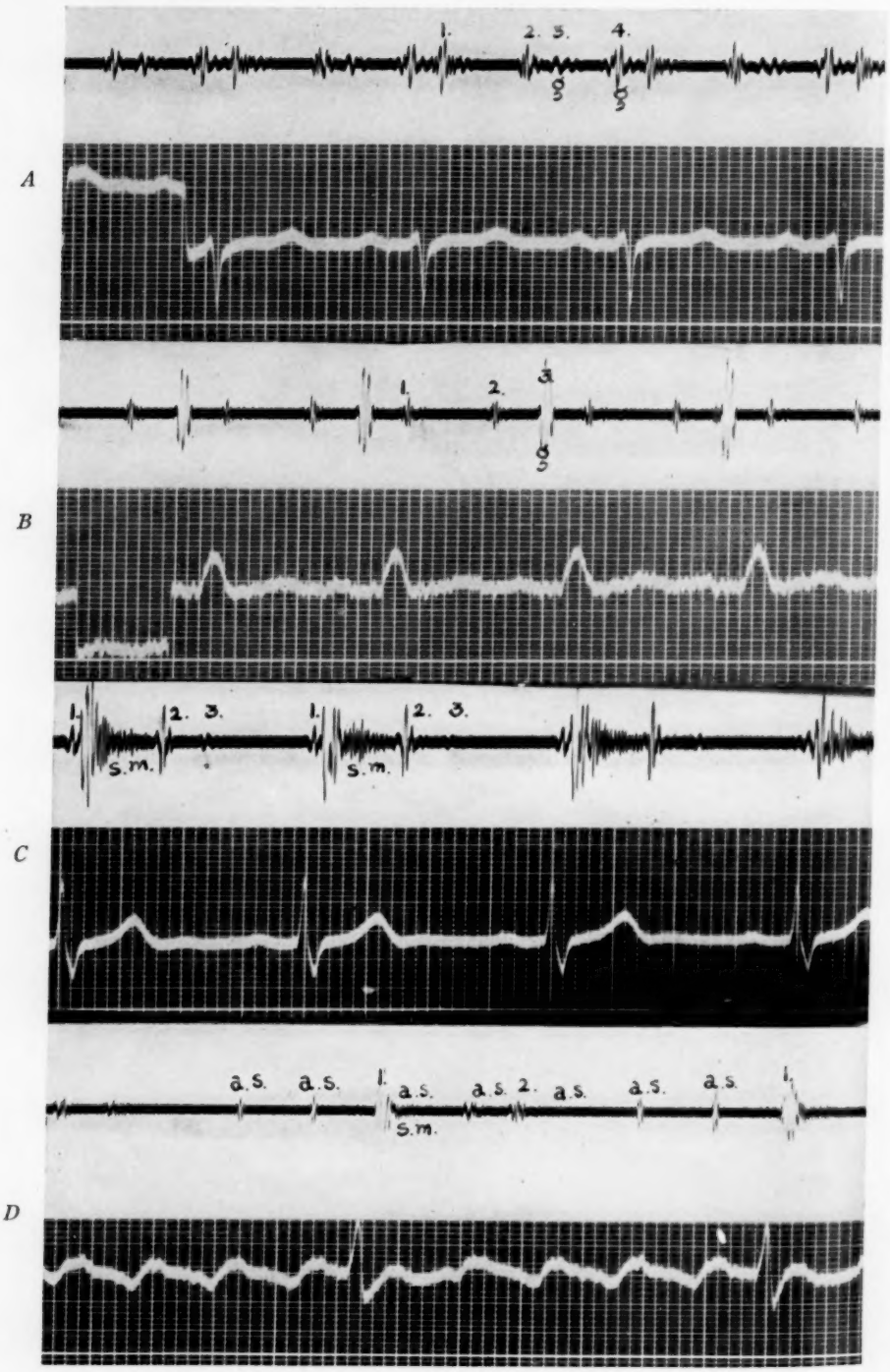
GALLOP RHYTHM

Gallop rhythm exclusive of systolic gallop is a clinical entity and implies established or impending heart failure.[8, 9] Graphically gallop rhythm is indistinguishable from the physiological third sound or from the fourth auricular sound.

Three different types of gallop rhythm are now recognized[8]: presystolic,

FIG. 3. *A.* Hypertensive heart disease with presystolic gallop. *B.* Systolic gallop in a case of possible organic heart disease. *C.* Protodiastolic gallop in active rheumatic carditis. *D.* Summation gallop with split first and second sounds in left bundle branch block.

S_1—split first sound. S_2—split second sound.


1. 2. 3. 4.
A
1. 2. 3.
B
1. 2. 3. 1. 2. 3.
S.m. S.m.
C
a.s. a.s. 1. a.s. a.s. 2. a.s. a.s. a.s. 1.
S.m.
D

protodiastolic and summation gallop. Both former types may coexist distinctly in one patient, and when the heart rate rises the two extra sounds meet to form summation gallop. The importance of systolic gallop or midsystolic click is still open to question. Clinical gallop rhythm must be distinguished from the occasional loud, presystolic or auricular sound heard frequently in the young, from the physiological third sound and from the opening snap in mitral stenosis. Rarely it can also be confused with a reduplicated second sound. Graphically the protodiastolic sound is distinguished from the opening snap in mitral stenosis in that the latter falls between 0.08 and 0.11 second after the second sound and is fairly constant in its location in the cardiac cycle, while the third and protodiastolic sound occurs 0.11 to 0.14 second after the second sound.

Among the 200 patients studied, clinical gallop rhythm was recorded in 26 patients. It was noted clinically and recorded graphically in 11 individuals among the 44 studied in the hypertensive group. It was described in five patients among the 70 in the rheumatic group; in five others among the 35 studied in the syphilitic group, and in five out of 26 in the coronary disease group. Whenever clinical gallop was noted it was almost invariably also recorded graphically. In three additional cases it was recorded graphically and was missed clinically in patients of established cardiac failure.

Of the 26 graphically confirmed clinical gallop, 40 per cent were protodiastolic in time, 40 per cent presystolic in time and 20 per cent were mixed and summation gallop. In only about half the number with gallop rhythm was there agreement between the clinical and the graphic record as regards timing.

Systolic gallop rhythm was recorded graphically three times but noted clinically only once. It occurred once in left bundle branch block in syphilitic aortic insufficiency and twice in patients among the potential or possible heart disease group.

Summary and Discussion

The graphic recordings of heart sounds and heart murmurs of 200 patients of organic heart disease were studied simultaneously and independently of their clinical records.

Based on established criteria which divide the normal sound from the ensuing murmur by the number of vibrations and time relation, and from a careful correlation with the clinical records of the individuals studied, it is concluded that graphic recording of sounds and murmurs cannot replace the trained ear. Indeed in many instances the ear is more trustworthy than

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Fig. 4. *A.* Presystolic and protodiastolic gallop in acute myocardial infarction. *B.* Presystolic gallop in intraventricular block with hypertension. *C.* Third heart sound and systolic murmur of mitral insufficiency of undetermined etiology. *D.* Auricular flutter in rheumatic heart disease with auricular sounds.

A.S.—Auricular sound. G—gallop.

the recording instrument. This is particularly true in short systolic murmurs of low intensity, and even more so in cases of soft, blowing diastolic murmurs of aortic insufficiency. The phonocardiograph cannot be relied upon for distinguishing functional from organic murmurs, any more than the ear alone can be relied upon. It is, however, in the third and fourth phases of the cardiac cycle that the recording instrument becomes of great value, since in a tachycardia it is frequently difficult, clinically, to place an extra heart sound in its exact position in the cardiac cycle, and often the extra sound is missed altogether, particularly when murmurs coexist. The fourth sound in such hearts is either not heard at all clinically or when heard is rarely placed in its precise position in the heart cycle. It is really in this phase of cardiac activity where extra sounds appear that graphic recording has greatly contributed. Phonocardiography is also of inestimable value in training the ear to greater acuity with reference to cardiac auscultation and as such should be of aid in teaching. Lastly, in being able to provide a record for future study at leisure and for comparison with subsequent tracings, the phonocardiogram serves the same purpose in relation to auscultation as a roentgenogram which supplements fluoroscopy.

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PROBLEMS OF ACUTE INFECTIONS*

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It is my pleasure today to speak to you concerning some of the problems which have to do with the everyday care of the patient sick with one or another of the acute contagious diseases. In this presentation I will not attempt to review the recent literature on the subject and will not endeavor to give you the last word in the experimental problems nor the laboratory studies of these diseases; I will simply attempt to give you a few of the diagnostic procedures which I have found of value and to discuss succinctly some of the methods of treatment I have employed in the contagious disease services at the Charity Hospital. I might add, furthermore, that I have drawn not only upon the cases that have occurred on my services, but also upon those that were on the services of my confrères, Dr. Tripoli and Dr. Stulb, in charge of the other two contagious disease services.

Scarlet Fever

Scarlet fever is one of the common diseases which usually are diagnosed without any degree of difficulty. However, in the milder cases the diagnosis is often extremely hard. Needless to state it is of importance to make the diagnosis because of quarantine-public health regulations. Scarlatina sine angina may be fairly common but I am always dubious indeed about the diagnosis of this form of scarlatina sine eruptione. Streptococcal invasion of the nasopharynx is quite usual in childhood. Whether these organisms are ordinary hemolytic streptococcus or whether they are the beta hemolytic streptococcus of scarlatina, it would seem to me a distinction without a very great deal of difference. The throat clears up in a short time with the use of sulfanilamide. I do not think there is any great likelihood of the child disseminating organisms and starting an epidemic if he is kept under partial quarantine for a few days. As a matter of fact, I think that the present regulations for the quarantine of scarlet fever are ridiculous. It does not take four to six weeks for a young patient to recover from the disease. Some years ago we were using antiserum and following its administration, to all intents and purposes, the child would be well in 24 to 48 hours. At the end of the week the throat would show absolutely nothing and we would discharge him. I have never heard of a single child we discharged conveying the organisms to another child but when the health

* A morning lecture at the Cleveland meeting of the American College of Physicians, April 2, 1940.

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authorities learned of this procedure they promptly made us discontinue, although they did reduce quarantine from six to four weeks.

In the diagnosis of the erythema the Schultz-Charlton reaction is of great value, but unfortunately it does not show up clearly in the dark skinned individuals, particularly of course the negro. The eruption of scarlet fever is characterized by formation of innumerable small papules. These papules can be observed readily by the simple procedure of taking a small pocket flashlight, holding it at almost right angles to the skin and close to it so the shadows of papules are cast on the skin. These papules then can be observed clearly and distinctly.

In regard to the use of serum, there is no question but that it is one of the most efficacious of the antisera. If a child is brought into the hospital in the afternoon and given the serum, the next day the rash will be gone, the temperature will be normal and the angina well on its way to a normal appearing throat. We have, as have many physicians in the past few years, discarded the use of serum except in the exceptional case, because this particular disease at this period seems to be on the downgrade in so far as severity is concerned. The disease runs a mild course; complications are few and far between. As a matter of fact we had not seen any severe septic cases for nearly five years, until last spring when we had three patients who were extremely ill, had marked adenopathy with pus formation and long continued fever. Because of the relative mildness of the disease and the prompt recovery of the patients, we, as many of the doctors with whom I have talked, felt that the almost invariable serum reaction which occurred after its use was more trouble-making and caused more disturbances than did the disease unmodified by serum. As has every one else, we have been using of late sulfanilamide in the treatment of these patients, as in all other infectious diseases. The results apparently are remarkable but it is hard to evaluate, as I said, because the disease is such a mild one nowadays the patient is going to get well promptly under any circumstance. To quote from the literature, Thenebe et al.[1] had more than 350 cases of scarlet fever treated with sulfanilamide and neoprontosil. Complications occurred in 9.7 per cent of their patients. Three-fourths of these were allergic or toxic. There is reduction in septic sequelae from 22.2 to 2.18 per cent. They recommend and we concur in this, the use of scarlet fever antitoxin when the sulfanilamide does not give satisfactory results which is only occasionally. They also advise that sulfanilamide be continued for seven or eight days in order to obviate septic complications. In an earlier paper by Wesselhoeft and Smith,[2] the contrary opinion is expressed. These authors do not think there is a reduction in the incidence of complications, nor is there very much effect on the toxicity, eruption and duration of fever.

In the study of the effect of sulfanilamide on the blood in scarlet fever, French [3] found that there was a constant slight depression of the total white count as a result of a diminution in the polymorphonuclears. She cautions

against the administration of sulfanilamide in a patient with a grave infection. Personally I would have no hesitancy in using sulfanilamide, watching the blood count closely and combining it with the antitoxin. Incidentally, I might comment on the diminishing likelihood of the antitoxin causing serum reaction. It is much more highly concentrated than it used to be, consequently these annoying reactions are diminishing.

Tularemia

I will speak of tularemia rather briefly because we observed a certain number of these cases in our contagious disease ward. We are fortunate that our cases are almost invariably of the glandular type. They come in with the initial lesion on the thumb or index finger, the adenopathy is pronounced and there is very little difficulty in making the diagnosis. Once in a while we have a typhoid type which is diagnosed entirely as a result of agglutination reactions. We also tried sulfanilamide in the treatment of a few patients. We have not had the results that Curtis [4] had, who claims the first report of the treatment of tularemia with his new drug. He had, in his patients with severe tularemia, a subsidence of the symptoms two days after administering sulfanilamide.

In the management of these patients there is one precaution which we are insistent upon, namely that the broken-down lymph glands be untouched. If the resulting abscess has to be opened this is not done until it is almost ready to break through the skin.

I place a great deal of reliance upon the blood agglutination reaction. We have had no experience with the antigen skin test as reported by Friedewald and Hunt.[5] This test is positive in the first week of the disease but nearly all of our patients with tularemia come into the hospital after they have been sick for a few days or longer.

We see many cases of meningitis but we have yet to see one of tularemic meningitis which was recently described by Kimmelstiel and Caldwell.[6]

Diphtheria

The incidence of diphtheria at the Charity Hospital, as elsewhere throughout the country, is diminishing, thanks to the almost universal Schick testing and use of toxoid. Some five years ago we undertook to immunize all children of school age in New Orleans. The campaign resulted in the immunization of some 40,000 children. This was then taken up by the Board of Health and the school authorities now insist a child must be immunized before going to school. The results of our campaign are shown by the following figures: In 1937, 150 children were discharged from the Charity Hospital with the diagnosis of diphtheria, 127 in 1938, 96 in 1939. Practically all of our cases now are children of pre-school age. It is definitely the duty of the family practitioner to immunize a child in early

infancy; certainly by the time the child is two years of age immunity should be conferred by the use of toxoid. What has been accomplished in some of the cities in the North, such as New Bedford, Providence, Rochester, Syracuse, Albany, Grand Rapids and Duluth, in controlling diphtheria is beautifully exemplified in the statistics published yearly by the Journal of the American Medical Association. Further illustrative of this is the experience recorded by Bundeson, Fishbein and White,[7] who found in 1917, for example, that there occurred slightly over 10,000 cases of diphtheria in Chicago, with a total number of deaths of 1,229 and a death rate per 100,000 of 47.8, whereas in 1937 there were 655 cases with 84 deaths and a rate of 2.3. These physicians recommend three doses of toxoid at monthly intervals. If it could be made a health law that all children must be immunized before two years of age, diphtheria would be almost a non-existent disease. Recently it has been suggested [8] that children be immunized not only with diphtheria toxoid but also with a combination of alum precipitated tetanus toxoid. This seems like an excellent suggestion.

In the Charity Hospital cases we are interested chiefly in those with laryngeal diphtheria and those children who have cardiac complications. The ordinary types of diphtheria yield promptly and immediately to diphtheria antitoxin with an average dose of 10,000 units. On the other hand, our laryngeal cases are children who die, sometimes from obstruction but more frequently from the complicating bronchopneumonia. They are usually all small children. In spite of enormous doses of antitoxin given intravenously or intraperitoneally and intramuscularly, usually dividing 80,000 to 100,000 units into two doses, one given intramuscularly, the other one or another of the other ways, the children die. At autopsy sometimes the diphtheria exudate will be found to extend down the trachea; sometimes casts of the trachea and the large bronchi may be lifted out bodily. Our results in this type of diphtheria are most distressing.

Cardiac complications are really most interesting. It is a moot question whether or not cardiac complications of diphtheria permanently injure the heart. Personally I do not think that in after-life the diphtheritic myocarditis of childhood will occasion heart disease in an adult. However, this question is of academic rather than of practical importance because the thing to be treated is the sudden acute heart failure which is often associated with vasomotor collapse which may cause sudden death in a child apparently convalescing satisfactorily and well on the road to recovery. Because we had several deaths in children who, although not supposed to be up and about, had gotten out of their beds and then died suddenly, we are very insistent upon a prolonged convalescence after diphtheria. I think this cannot be stressed too forcibly. If a child has a slight tonsillar lesion and is given antitoxin, the exudate disappears in two or three days, the cultures are negative in a week and the child has not appeared particularly sick; it is difficult to insist that such a child should be kept quiet for three weeks and

no active exercise permitted for four weeks. For a period of time we attempted to control the length of convalescence by electrocardiograms but this proved to be impractical because of the size of the service. Now we caution the mother, if the child is discharged, not to let him go about and play and enter into the usual childhood activities of a well child. Certainly this is a precaution which every physician will insist upon did he see occur in his practice the sudden death of an apparently satisfactorily convalescing child.

In the treatment of cardiac failure we lay a good deal of stress on the administration of glucose, depending on it rather than upon digitalis which may be actually contraindicated in certain types of heart failure, or upon caffeine and similar drugs.

Measles

During the winter of 1927–28 there was an extremely severe epidemic of measles in the City of New Orleans. This epidemic became so severe and so large was the number of cases that for the only time in my knowledge it was possible to admit to the Charity Hospital only the patients with measles who showed complications. Ordinarily one looks upon measles as an extremely mild disease, one which it is advisable for the child to have before school days, so as to get over with it and to be subsequently immune. One who has gone through a severe epidemic of this disease dreads the possibility that this usually endemic disorder may obtain epidemic proportions. At this time on my service alone there occurred 351 cases. These figures can be contrasted with the incidence of measles in the Charity Hospital on all services in the last three years. In 1937 there were 67 cases; in 1938, 98; in 1939, 96. The mortality was practically nil, two children died but they already had some other complicating condition. On the other hand, during the severe epidemic the children were dying from complicating bronchopneumonia, otitis media with its complications, and a few from encephalitis. As a matter of fact, in the cases of children of two years of age or under, bearing in mind that they already had severe tracheobronchitis when admitted to the hospital, it was almost the exception rather than the rule that they would recover.

During this period of time we were able to obtain six consecutive blood cultures which were positive to an organism which fulfilled Tunnicliff's requirements in every way. We felt very definitely at that time that the condition was due to the specific organism. There is a question whether measles is due to a specific organism or is the result of a virus infection. It seems to be the general feeling among medical men at the present that measles is a virus disease. It might well be possible to have obtained the diplococcus of Tunnicliff by blood culture at this time because it was a secondary invader. Certainly in subsequent blood cultures we have not been able to confirm her work. As further evidence that measles is possibly a virus disease is

the fact that encephalitis is by no means an uncommon complication. In 1928 Hauser and I [9] reported on eight patients with encephalitis who died, reporting on the autopsy findings in two of these cases. In addition to the eight fatal cases, all of which showed the presence of numerous discrete, punctate hemorrhages throughout the brain grossly, with perivascular hemorrhage around many of the small vessels microscopically, we also had a goodly number of patients who recovered. That this complication is not rare in epidemic measles is further substantiated by a communication from Peterman and Fox.[10] They observed an epidemic in 1933 when there were 13 cases of this complication, and in 1938 there was another epidemic of the disease with 14 instances of postmeasles encephalitis. This complication is associated with a fairly definite syndrome which is expressed by the onset of cerebral involvement on or about the fourth day after the rash has come out. There occurs rigidity in the muscles of the neck, stupor and convulsions. There is a leukocytosis, the spinal fluid is under increased pressure and shows an increase in the number of lymphocytes. The mortality rate, according to these observers, is roughly 30 per cent.

The other complications of measles, otitis media and bronchopneumonia are extremely common. On the other hand, noma is very rare in my experience. I have seen only one patient with this disorder.

The treatment of measles has been good nursing care and that is about all. I have not had the opportunity of using sulfanilamide or sulfapyridine in the complicating bronchopneumonia. In view of the horrible experiences during the great war with streptococcic pneumonia following measles which resulted in the death of many thousands of soldiers, it might be advisable to use this drug should an epidemic arise, irrespective of whether or not the young person has any complications. It might possibly forestall streptococcic pneumonia.

My experience with the use of convalescent serum has been extremely limited; as a matter of fact the little information I have about it is largely from hearsay. I have from time to time requests from doctors for blood serum of children convalescent from measles for use in sickly, undernourished children who have been exposed to the disease or who are living in an epidemic. The results have been excellent, again from hearsay, the serum distinctly modifies the severity of the disease and sometimes apparently prevents it. I believe almost equally efficacious, however, is whole blood given in quantities two or three times greater than the amount of immune serum. The whole blood can be gotten from nearly any adult who has had the disease and whose blood need not be compatible because it may be given into the muscles of the buttocks and thigh either defibrinated or else unchanged. There is now on the market a measles antibody preparation known as immune globulin obtained from human placental blood and tissue, placental blood apparently transmitting antibodies in greater number than normal blood. The advantage of the preparation is, of course,

that it is always on hand, whereas convalescent measles patients are not always available and to a small baby giving whole blood would require a greater amount than it might be possible to inject comfortably. In a recent article McKhann [11] reports that placental extract had been used in 2740 cases. He was able to protect 1762 (64.3 per cent) patients, modify the course of the disease in 833 (30.4 per cent), while it had no effect in 145 instances (5.3 per cent). From the work of the Massachusetts observers (McKhann, Eley and others) it would seem to be definitely established that this commercial globulin given in doses of 2 c.c. is of immense value in preventing and modifying measles. As I said, I have had no experience with it or with protective doses of serum because the measles patients I see already have their disease fully developed.

Measles frequently happens in the newborn provided the mother has not had the disease. I have seen infants emerging from the birth canal with a rash in the same stages of development as on the mother. There seems to be a popular conception that because immunity to measles is given by the mother to the child for a period of six months to a year, such immunity can exist irrespective of whether or not the mother has had the disease. If she has not had measles the child will not be protected.

Kohn, Fischer and Resch [12] have checked over the value of parenteral whole blood in the treatment of measles after the rash has appeared. They were unable to find any variation as to the severity of measles in the control group of 758 children, as compared with the test group of 76 children.

Whooping Cough

A great deal of interest in immunizing against pertussis has been aroused in recent years, largely by Sauer,[13] who has prepared a special vaccine which apparently produces a more or less permanent immunity within a period of some three months. I have had no experience with Sauer's vaccine because when I see the children the disease is already fully developed. I have, as with measles, given to some of my doctor friends convalescent serum from patients on the contagious disease service. They have been skeptical after using it, about the value of convalescent serum in preventing or ameliorating whooping cough. Lucas [14] writes that the passive immunity, lasting not more than three weeks, which is conferred by convalescent serum, is a more effective agent than vaccine in the prevention of whooping cough in children already exposed.

The lymphocytosis which occurs in whooping cough is very well known. Sometimes the total count and the number of lymphocytes increase to remarkable figures. Several years ago we had a child who for some three weeks had a total leukocyte count which remained persistently over 125,000, 99 per cent of which cells were lymphocytes. Needless to state such a picture resembles very closely leukemia but this child's count gradually returned to normal in about six weeks.

Here is a method we find quite efficacious in controlling severe paroxysms of coughing. Ten or 20 c.c. equal parts of olive oil and of ether are injected into the rectum. This is an irritating, burning solution so that the cheeks of the child's buttocks must be held together for several minutes lest the material be expelled. It is definitely beneficial and well worth trying in refractive cases.

For a period of nearly a year all of our patients were treated with roentgen-ray. We could not see any improvement in the length of illness, severity of the cough or control of complications.

Chickenpox

Measles is often referred to as the most contagious of contagious diseases but as a matter of fact chickenpox is much more contagious. I have seen 149 cases of chickenpox in the last three years. Practically every child gets it sooner or later after maternal immunity has disappeared. As with measles, chickenpox may occur in the newborn baby if the mother is not immune. Witness the case reports of Campbell [15] and Shuman.[16]

The only complication or sequel of any moment in varicella is the secondary infected pox on the face of girl babies and small children. So that they may not scratch the facial lesions we have been accustomed to put a tongue-depressor splint at the bend of the elbow so that the arm cannot be flexed. Recently we have used a very simple contraption of a pasteboard cuff about the elbow joint which can be taken off and put on very much more readily than the splint and which will serve the same purpose.

Erysipelas

On the Charity Hospital contagious disease services there have been admitted in the past three years 197 patients suffering from erysipelas. These patients do not present, as a rule, any marked diagnostic problem. Occasionally the patient may have a cellulitis which is non-specific but as a rule the diagnosis is obvious. There are admitted a certain group of patients who have the so-called recurrent erysipelas. I do not believe that these patients should be classified as true cases of erysipelas. The usual story is that in the past they have had erysipelas, usually of the lower extremity and frequently developing from around a leg ulcer. The patient has sudden fever without prodromes, the area of previous involvement becomes a red to dusky red, the overlying skin is indurated and to all intents and purposes acute erysipelas is present in that extremity. However, within 48 hours the temperature will have subsided, there will have been no extension of the lesion and the skin itself becomes soft and pliable. I believe that these flare-ups represent allergic phenomena in skin previously sensitized, as shown by Amoss, which responds to the presence of an antigen, the specific streptococcus, which has gained entrance somewhere into the

body, most likely in the upper respiratory tract. It may be that some other streptococcus other than a specific one may produce the same result. This is an annoying sequel of erysipelas. In one instance an elderly man was readmitted to the hospital nine times in the course of a year. He was finally persuaded to stay home, rest for 48 hours and not worry about his condition, otherwise I believe he would have kept on coming into the contagious disease ward interminably.

On the whole the results that have been obtained on our respective services with specific antitoxin have not been particularly brilliant. This may be because many of our patients do not enter the hospital until after they have been sick for three or four days. Under any circumstance injection of 40,000 units or more of this antitoxin has not had a very appreciable effect on the severity of the disease nor any outstanding effect on its course.

One of the objectives in the management of the patient is to prevent the spread of the infection of the skin. At one time the older physicians awaited the stopping of the infection at natural boundaries. At one time they used tight adhesive strips placed 1 or 2 cm. above the extending inflammation. A very satisfactory method I have found to stop the spread of the lesion has been to inject the specific antitoxin intradermally about 3 or 4 cm. above the elevated reddened skin, bearing in mind that the causative organism is a centimeter or more ahead of the inflammatory reaction. A wheal is produced; at the base of this wheal another wheal is produced; this is repeated until the inflammation is completely circumscribed. By this method it has been possible to limit the extension of the disease process.

The modern treatment of erysipelas is by the use of sulfanilamide. We have treated now some 40 patients with erysipelas with sulfanilamide and have had excellent results. Following a large initial dose we give 1 gram every four hours to the average adult patient, omitting one dose at night. With the sulfanilamide an equal amount of sodium bicarbonate is given. The disease comes to a relatively abrupt cessation in two or three days. Sometimes the results are quite spectacular. We have been maintaining smaller doses of sulfanilamide following the cessation of fever and the extension of the inflammation for three or four days and cutting down approximately to about one-half the dose maintained when the patient was febrile.

Acute Lymphocytic Choriomeningitis

We have had in our hospital services a series of patients, 12 in number, who suffered from this virus disease which has been considered to be a rather relatively rare condition. This group of cases has been reported by Tripoli and Fader.[17] The virus that is responsible for this condition is capable of being transmitted to monkeys, guinea pigs and other experimental animals by a variety of routes. The disease is transmitted by direct in-

oculation. Toomey [18] reported on 70 patients to whom apparently the virus was transmitted with a considerable degree of contagiousness.

It is rather interesting that this disease, which was first recognized by Wallgreen,[19] has become a rather prevalent disease. Cases have been reported from various parts of the United States as well as from Europe and Australia.

Postmortem findings are almost unknown because people with this condition do not die.

The clinical syndrome is one of relatively mild prodromal symptoms, followed by a quite abrupt onset which suggests very strongly the onset of meningitis, there being nausea and vomiting, high fever, headache, disturbed psyche, and rigidity of the muscles of the neck. Given a patient who is apparently suffering from acute meningitis the lumbar puncture is performed and it is found that the cell count ranges from 250 to 1000. Stiffness of the neck was present in all cases reported by Tripoli and Fader. The spinal fluid was under slightly increased pressure and the differential cell count showed from 50 to 100 per cent of lymphocytes. It has been our experience that very promptly the diagnosis is made of tuberculous meningitis. Then the patients begin to improve. They develop no cerebral or nervous complications. The duration in this series of cases ranged from five days to 16; in only three instances did the disease last longer than 10 days. The only treatment that was employed was drainage of the spinal canal from time to time. This might be said to have been more for the purpose of obtaining spinal fluid for study than for real treatment.

The most satisfactory feature of this condition is the intense relief the doctor feels when, in the course of two or three days, the patient he thought had tuberculous meningitis, proceeds to improve. Instead of going on to death he gets well rather rapidly.

I am rather of the impression this disease is more frequent than can be shown statistically. I believe it is quite possibly present in patients who have fever, headache, drowsiness and show some slight rigidity of the neck. They may be accused of having any one of a number of acute infections, possibly grippe in most instances. They are not extremely ill and so lumbar puncture is not done and without the spinal fluid survey there is no positive evidence to indicate that this condition is present. If spinal fluid examinations were done routinely just as are leukocyte counts, maybe there would be a marked accretion in the number of cases. This would at least be of epidemiologic interest.

Pneumococcal Meningitis

One cannot but help being enthusiastic about sulfanilamide and sulfapyridine. The outstanding and astounding results with the use of these drugs in some of the severe diseases and infections make it impossible to

blame a man for being hyperenthusiastic. I do not know of any disease in which the beneficent effects of the drug are better exemplified than in pneumococcal meningitis. When I had a patient come into the ward with signs of meningitis and when the thick inspissated spinal fluid of pneumococcic meningitis was drawn out through the lumbar puncture needles, my reaction promptly was to say the patient would be dead in a very short time. Within the last six weeks there have been on our contagious disease services six patients with pneumococcal meningitis; four of them have recovered without a single complication. Their recovery has been prompt and dramatic. The drop in temperature has been almost by crisis. Bear in mind that these patients were extremely ill when they came in. A number of them were in coma and unconscious on admission to the hospital. The incident of a small boy, for example, will illustrate what has happened in every case. This child could not be aroused; he was actively delirious. Early the morning after admission the delirium had subsided to a great extent although he still had to be restrained, but by the middle of the morning he could be aroused so he could understand what was going on. The next day the sensorium was entirely clear and from then on he proceeded to get well. Of these six patients, four survived, and two died, both of whom succumbed very promptly on admission to the hospital. One died within four hours after admission, the other patient had been sick for several days before he entered the ward.

Fortunately meningitis in its acute onset is characterized by an obvious and marked symptomatology. The patients are severely ill, they are admitted without delay to the hospital so that they can be treated early and treatment is not put off for several days or longer as it may be with typhoid fever or even with erysipelas. Every one has agreed that the earlier the sulfapyridine is administered the greater is the chance for recovery.

We have not been limiting our treatment entirely to sulfapyridine. We have also used specific serum in every instance except one, but we have used specific serum before and have never had the dramatic and spectacular results that have been obtained with the serum and sulfapyridine combined. It looks very much as if the sulfapyridine was the important factor. The therapeutic regimen has been as follows: The spinal canal is drained and such drainage is repeated every six or eight hours until the spinal fluid is clear or the cell count is markedly diminished and there are no signs of intracranial tension. The patient is given, as soon as the diagnosis is made and the serum typed, the specific antitoxin intravenously. The patient is also given sulfapyridine either by mouth, which in most instances he cannot take, or else the soluble salt intramuscularly.

Meningococcic Meningitis

The diagnosis of meningitis is fortunately relatively simple. A patient presenting headache, a clouded sensorium, abrupt onset of symptoms and

rigidity of the neck is subjected to spinal puncture. The diagnosis of the specific type of meningitis is made by laboratory methods promptly so that meningococcic meningitis is one of the diseases that are early recognized by the physician. Occasionally a patient is seen in whom the symptoms are not pronounced. I remember very well indeed a young girl who was pregnant and presented a low degree of fever. Every possible type of laboratory examination was made in order to discover the cause of the fever. Finally after a week or ten days some bright diagnostician came along and suggested a spinal puncture which was done and turbid fluid obtained. The patient was transferred to the contagious services at Charity Hospital and proceeded to recovery uneventfully, about three months later giving birth to a healthy child. Lumbar puncture, of course, is the important procedure in making the diagnosis. Stiffness of the neck is the only physical sign early in the course of the disease that is of any moment. Kernig's sign is absolutely worthless except for its negative value.

In the treatment of our meningococcic meningitis patients we have been running the gamut of therapeutic procedures from those suggested by others, to those which we have devised ourselves. Tripoli [20] reported several years ago on a considerable series of cases. Serum was used intramuscularly, intravenously, intraspinally, Prengle's iodide was injected in the carotid, continuous drainage through combined cistern and lumbar puncture was employed together, in combination or singly, and always our results have been rather poor. About 50 per cent of our patients have died, a higher incidence than was being obtained at the same time in New York as Josephine Neal brought out in her discussion of Tripoli's paper. Of late we have been using antitoxin intramuscularly and intravenously. I would suggest that the first dose be given intravenously with, of course, the usual precautions appropriate to the giving of any intravenous injection of serum, employing 20–30,000 units diluted to 200 c.c. with normal salt solution. The injection should be given slowly, and simultaneously the same sized dose of serum should be given intramuscularly. This dose is repeated according to the reaction of the patient in 24 hours. It may be diminished as the patient improves. As a rule it is not necessary to give more than 100,000 units intravenously. At the same time sulfanilamide is started. If the patient is delirious and is unable to swallow, sodium sulfanilamide is injected intramuscularly. The initial dose is approximately 4 to 6 grams, depending on the size of the patient. This is repeated in four hours and thereafter a gram is given every four hours until the patient starts to improve. Then the quantity of sulfanilamide is gradually diminished but still continued for three or four days after the temperature has come to normal.

In a disease which varies so much in its severity, in which at one period practically every case results fatally and in which at another period all pa-

tients get well, it is impossible to state definitely that the above form of treatment is unusually effective. In the last three months our results have been perfectly splendid. It might be that we are too optimistic and that in the presence of a more virulent type of meningococcus the results may not prove as satisfactory.

Serum is not used intraspinously but the spinal canal is drained twice in the first 24 hours, thereafter once or twice in the next 24 hour period and then daily or bidaily, depending on the amount of fluid obtained and the pressure under which it emerges.

I do not think that the physician should weigh too heavily the dangers of active treatment in the case of meningitis irrespective of the bacterial cause. He is dealing with a condition in which the odds are in favor of death. He cannot afford to temporize or to delay. Chances must be taken, which chances incidentally I believe are overstressed. Certainly my experience with sulfanilamide and sulfapyridine have not indicated that more than the very exceptional patient reacts badly to this therapeutic agent.

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THE PROBLEM OF RHEUMATISM AND ARTHRITIS

REVIEW OF AMERICAN AND ENGLISH LITERATURE FOR 1939

(Seventh Rheumatism Review) *

Part II

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CONTENTS

Part II

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Hypertrophic (Osteo-) Arthritis

Hypertrophic arthritis was regarded, not as one disease, but as a pathologic "pattern reaction" to different articular insults.[178, 283] McMurray divided his cases of osteo-arthritis of hips thus: (1) unilateral, those in which a hip was affected by chronic trauma incident to a congenital or acquired malformation, or by single acute trauma; (2) bilateral, those in which both hips were "spontaneously" affected. [We would label the first group "secondary hypertrophic," the second group "primary hypertrophic arthritis."—Ed.] Fletcher listed his cases thus: general osteo-arthritis [i.e., primary hypertrophic arthritis—Ed.], traumatic osteo-arthritis, occupational osteo-arthritis, osteo-arthritis of spine, osteo-arthritis associated with gout, osteo-arthritis leading to infective arthritis [not defined—Ed.], infective arthritis leading to osteo-arthritis [apparently meaning the late hypertrophic changes which may occur in atrophic arthritis.—Ed.]

Primary Hypertrophic (Senescent, Degenerative, Osteo-) Arthritis

Clinical Data. Joints affected in Monroe's 466 cases were: knees in 60 per cent, fingers in 52 per cent, lumbar vertebrae in 50 per cent, cervical vertebrae in 45 per cent, shoulders in 43 per cent, thoracic vertebrae in 30 per cent, hips in 30 per cent, sacro-iliac joints in 30 per cent, "feet (static)" in 15 per cent, temporomandibular joints in 0.5 per cent. Heberden's nodes affected women nine times as often as men in Monroe's series; 93 per cent of Burt's 40 consecutive patients with Heberden's nodes were females. Fingers affected were in order of frequency: right index in 85 per cent of cases, right middle in 58 per cent, left index in 48 per cent, left middle in 43 per cent, right and left "ring finger" each in 38 per cent, and right and left "little finger" each in 33 per cent.

The pain of hypertrophic arthritis has never been adequately explained. The pain of Heberden's nodes is due, according to Bauer [50] to periosteal elevation from rapid proliferation of marginal osteoid tissue; when the latter occurs slowly, or ceases and marginal osteoid tissue becomes calcified, pain ceases. Other causes of pain are altered mechanics, impingement of pedunculated villus, loose bodies (Bauer), pressure on pain sense organs in bone, vascular congestion in subchondral bone, congestion or edema of irritated synovial tissues (Collins). Stamm distinguished six types of pain in hypertrophic arthritis: (1) that from bone sclerosis which is a deep boring pain unaffected by rest or activity, worse when the part is warm, e.g., at night; (2) that from adhesions and capsular fibrosis which is relieved by rest, aggravated by activity, worse at the day's end; (3) that from nipping of soft parts, a sharp, momentary pain relieved by rest, present only during activity and located at the opposite side of a joint from pain caused by stretching of adhesions; (4) pain from the grinding together of rough surfaces; such pain is present only when movements are made "under load," and is relieved by rest or traction; (5) pain from chronic articular trauma or from associated fibrositis; such pain is associated with stiffness after

resting, relieved by moderate activity, aggravated by more activity; (6) referred pain such as pain in knee from an arthritic hip, sciatica with spinal arthritis.

Premature Hypertrophic Arthritis. Ordinarily hypertrophic arthritis affects only persons over 40 years old, but premature cases are not infrequent. Of Monroe's patients 30 per cent had the disease before the age of 40 years; 12 patients were under 20 years of age. Two unusual cases of premature hypertrophic arthritis were reported.

A girl, aged 15 years, who had marked Heberden's nodes, was noted by Burt; parents were not similarly affected. Polyarticular osteo-arthritis of five years' duration in a man aged 29 years was described by Thomson: hips, knees, shoulders, elbows, wrists and spine were grossly affected; motion was limited but painless; loose bodies were present in shoulders and hip joints [but not elsewhere, hence the case was apparently not one of osteo-arthritis secondary to osteochondromatosis.—Ed.] Thoracic vertebrae showed herniations of nucleus pulposus. Roentgenograms of long bones revealed irregular deformities (fusiform enlargement of femoral and humeral heads, thinning of bone cortex, accentuation of longitudinal striations) suggestive of a disturbance of the growth of the "cartilage-formed bones" rendering them hypersensitive to ordinary stress and strain. From a knee loose bodies were removed and synovia examined: synovial membrane and marginal cartilage were thickened and actively proliferating, chondrophytes being prominent; chronic inflammation and fibrosis were present but no pannus.

[The sedimentation rate was not given. One of us, P. S. H., has seen a similar case: marked hypertrophic polyarthritis of 17 years' duration in a physician aged 34 years, with loose bodies in some joints only; articular motions which were limited, were painless in some, painful in other joints. There has been no loss of weight, flexion deformities or muscle atrophy; sedimentation rates were repeatedly normal. The hypertrophic changes in roentgenograms were marked, resembling those of a senescent patriarch.—Ed.]

Roentgenograms. No new data were reported.

Pathology. This was reviewed by Bauer and Collins.

Laboratory Data. Sedimentation rates are usually normal, occasionally abnormal for unknown reasons [50, 310]; rates were elevated [degree unstated] in 17 per cent of Fletcher's 103 cases. Serum phosphatase is normal,[728] but may be lowered by therapy with vitamin C.[707] Patients with obvious hypertrophic arthritis who have an elevated serum phosphatase should be examined for malignancy [an important point—Ed.]. Serum proteins are normal or only slightly altered.[671] The average total synovial fluid nucleated cell count is 500; it seldom exceeds 2000 per cubic millimeter; the percentage of polymorphonuclear leukocytes is 10 per cent or less (Bauer).[50]

Etiology: 1. Factor of Tissue Senescence. Collins [178] considered the cartilage changes caused by simple degeneration of advancing years.

2. Factor of Trauma. The wear and tear of long continued trauma was blamed by the majority. "Osteo-arthritic changes in a joint are always and only of mechanical origin" (Stamm). Burt blamed occupational trauma (e.g., needlework, washing), for the production of Heberden's nodes; they "are most often found on the fingers most used." Industrial trauma [512] and abnormal posture [480] were also blamed. "The deeper the hip socket, the greater is the proclivity towards osteo-arthritic degeneration" of the hip,

according to Gilmour. A deep hip socket alters the hydrodynamics of the joint; the hydraulic buffer formed by synovial fluid apparently cannot act like a shock absorber, and hypertrophic arthritis develops from mechanical friction.

3. Factor of Impaired Circulation. Joints and blood vessels of 13 lower extremities amputated for gangrene from arteriosclerosis of thromboangiitis obliterans were studied by Kling. Synovial vessels were essentially normal; degenerative arthritis was noted only in old joints and bore no relationship to vascular changes; hence the vascular theory was "contradicted."

4. Factor of Endocrine Dysfunction. Among Potter's 33 cases metabolic rates were normal in 15, above normal (over + 10 per cent) in five, subnormal (under — 10 per cent) in 13 cases. "Uncorrected rates" were normal for 63 per cent of Rawl's 111 clinic patients, for 43 per cent of 14 private patients; in the rest they were above, oftener than below, normal. Among Monroe's 149 cases metabolic rates were below — 10 per cent in 43 per cent. Bauer [51] noted subnormal rates no oftener than in any group of cases of similar age: "Certainly there exists no proof for the various metabolic, endocrine, circulatory, infectious and toxic theories" of hypertrophic arthritis.[50] But Kling considered "imbalance and dysfunction of the endocrine system and especially a preponderance of the hypophysis at the menopause" an etiologic factor [no proof given—Ed.].

5. Factor of Altered Metabolism. Transient hypertension was not uncommon in Monroe's cases; blood pressure in Weber's cases averaged 142/86 and the mean weight was 162 pounds, 16 pounds more than that of patients with atrophic arthritis. Among 103 cases of "general osteo-arthritis" Fletcher found obesity eight times as often, hypertension four times as often, as in the general sick population. The incidence of hypertension was not wholly dependent on obesity: 37 per cent of the osteo-arthritics of normal weight had hypertension; 42 per cent of the hypertensive arthritics had normal weight. Of the 103 patients 25 were only obese (at least 20 per cent overweight), 26 had obesity and hypertension, 19 had hypertension without obesity. The menopause did not seem to be an important factor. But since obesity and hypertension are presumably related to endocrine abnormalities Fletcher concluded that "an endocrine dyscrasia may be one of the 'triggers' which produce the pattern" of osteo-arthritis.

[This paper, written for the first award of the Heberden medal, is rather disappointing in that it contains little "meat" but much hypothesis, mostly as to the causes of obesity and hypertension rather than of hypertrophic arthritis. As to the influence of the menopause the writer seems to contradict himself, and he seemed to be uncertain of his own conclusions.—Ed.]

No notable abnormalities in sulfur metabolism were found.[184, 811] Most of the 21 patients of Sherwood and Thomson were on diets deficient in calories, protein and minerals but not in vitamins; despite this the vitamin C content of blood was generally subnormal. According to Traut and Vrtiak

allergic manifestations (asthma, hay fever, urticaria, eczema, migraine, rhinitis) affect patients with hypertrophic arthritis oftener than normal persons or those with atrophic arthritis.

6. Factor of Infection. The infective theory was supported by Crowe and his colleagues.[207] Based on his studies on streptococcal antibodies Levinthal conceded a relationship to streptococcal infections in some cases of hypertrophic arthritis. But the leukopenic index after intravenous injections of "streptococcal substance" was normal in the cases of Hicks and Wyatt.

7. Neurogenic Factor. "The amount of pain and stiffness exhibited by a case of osteo-arthritis depends just as much on the attitude toward life as on the degree of bony or ligamentous change disclosed by the radiograph, perhaps even more" (Gordon). The previously mentioned conclusions of Stein-Lewinson applied to cases of hypertrophic as well as atrophic arthritis. (See Etiology of atrophic arthritis, psychogenic factors.)

Treatment. Weight reduction diets were advised in obese cases.[32, 386] The supposed value of a raw vegetable, fruit, cereal and milk diet was discussed.[599] "Vitamins are harmless and may be used if the spiritual support of pills is required."[542] Vitamin D in concentrated doses was recommended by some.[693, 707, 758] Injections of sulfur reputedly gave some subjective improvement.[184, 282, 811] Gold therapy produced no cures, "good results" in 20 per cent, "fair results" in 25 per cent, and poor results in 55 per cent of the 20 cases of Snyder, Traeger and Kelly; others[650] considered it of little or no value. Results from Crowe's vaccine[206, 207] were as follows: of 1062 patients treated by Crowe 7 per cent became symptom free, 41 per cent were "much improved," 35 per cent were "improved," 17 per cent were unrelieved. Of Voss's 62 patients so treated 21 were "much improved or cured," 18 improved, 23 unimproved. Weiner considered "specific" and nonspecific vaccines, given without febrile reactions, of doubtful value. Stanley favored the use of chaulmoogra oil. Bee venom seemed valuable to Ainlay but not to Mackenna. Thyroid extract was considered a "valuable adjunct."[616] Fletcher[282] tried to reëstablish the use of iodine.

[The results given in all of these papers impressed us very little.—Ed.]

Intra-articular injections of lactic acid were recommended by Waugh for reasons already given (see treatment of atrophic arthritis: surgical orthopedic measures); 12 patients with hypertrophic arthritis were "improved" thereby. Stamm recommended roentgen therapy for the deep boring pain presumably caused by bone sclerosis, but reported no results. Local roentgen therapy for peripheral osteo-arthritis, and widefield roentgen therapy for spinal arthritis were again advocated by Scott; results were "very good" for knees, "satisfactory" for smaller joints, "very satisfactory" in cases of spondylitis. [Scott has not yet given his results in statistical percentages.—Ed.] Eidenow noted no real effect from roentgen therapy, only some analgesia.

Fever therapy gave significant relief in only three of Ferderber's eight cases; in 14 per cent of 128 cases of Davison, Lowance and Crowe. It was not recommended by Neymann. Results from acetyl-beta-methylcholine chloride seemed poor to some,[458] fair to others.[92] The advantages of infrared,[776] short wave therapy[113, 197] and fangotherapy[787] were noted. Proper shoeing, the use of foot plates,[476] bandages for knees, Thomas heels and exercises for quadriceps muscles were discussed.[340] Local injections and regional anesthesia with procaine solutions were strongly recommended by Steinbrocker.

For painful hips Green[340] and Stamm considered traction at night useful, but according to Fisher the pain in hypertrophic arthritis is due generally to contractures of capsule and periarticular tissues, rarely to apposition of articular surfaces; hence caliper splints and other measures to separate articular surfaces are rarely indicated.

Manipulation had its advocates.[57, 58, 278, 529, 594, 723] Stamm used it (under anesthesia) to relieve pain due to adhesions, capsular fibrosis and to nipping of soft parts; others used it for painful stiff hips,[278, 529, 594] but Douthwaite saw no rationale to it; in his opinion it generally does not relieve affected hips but may relieve associated fibrositis. Complete relief of pain was provided by Burns in eight of 12 cases of hypertrophic arthritis of hips by fixation with a Smith-Petersen pin; a method of performing this operation without exposure of the joint was described.[36] Since synovial membrane is rarely much affected in hypertrophic arthritis, synovectomy is indicated only in late cases if the membrane is thickened and thrown into folds at the periphery of the joint; partial synovectomy to remove papillary masses of granulation tissue may then relieve pain and improve function (Swett). In three cases of hypertrophic arthritis of knees excision of patellae was done by Berkheiser with apparent improved function. Selig recommended arthrodesis in some cases when one hip is affected, unilateral osteotomy for a patient with both hips affected who refuses fusion of one; he considered arthroplasty of hips inferior to fusion; acetabuloplasty and drilling (forage) were considered of uncertain value.

Since degenerating cartilage is never replaced by normal cartilage a cure of hypertrophic arthritis is impossible.[50, 542] "The disease stops only with death," but the foregoing measures may retard the process, relieve pain and improve function. Monroe's follow-up study of 331 cases showed "good results" in 53 per cent, "improvement" in 32 per cent, no results in 15 per cent.

Backache and Sciatica

General Remarks on the Causes of Backache and Sciatica. The literature under review included almost 100 papers on these subjects, among them general articles on the causes of backache, the technic of examining patients therewith,[290, 295, 420, 457, 553, 680, 791] and the special roentgenographic examina-

tions often required.[61, 151, 349] A roentgenographic study of spinal mobility was made by Elward who suggested revision of some current ideas thereon. It was disproved that flexion is freest in the lumbar region. The spinal column is not a single hinge but many interacting hinges; there is no single center of motion, except the mass motion of flexion centering in hips; there are numerous centers of limited motion. Structures of the back are so interrelated that disease of one may produce disease in another; hence several different conditions may produce rather similar symptom complexes. Differentiation can only be made by careful physical and roentgenologic examinations; no one orthopedic maneuver or "test" is pathognomonic of one spinal condition.[231, 290]

Physicians again disagreed as to which are the commonest causes of backache. Some[427] said strain; others[553] incriminated arthritis, poor posture and trauma in that order. Owen's order of indictment was infections, acute or chronic trauma, poor posture, congenital anomalies and intraspinal lesions (herniated disks, tumors, fractures).

Backache from Urologic Lesions. No data thereon came under review.

Backache from Gynecologic Lesions. No new data were reported.

Backache from Gastrointestinal Disease. Back pain caused by peptic ulcer, gastric cancer and diseases of gall-bladder, liver, pancreas, appendix and colon were briefly distinguished: in general the eating of food affects this type of pain.[545]

Backache from Disease of Interspinal Ligaments. The interspinal ligaments connect adjoining spinous processes; they are stretched in flexion and function constantly. Macey described an unreported type of backache, a localized painful region between two or more spinous processes; pain was aggravated by flexion and not relieved by usual conservative therapy—heat, massage, etc. Tenderness to pressure was superficial; roentgenographic, neurologic and orthopedic examinations were negative. In one case of five years' duration, pain began after the strain of childbirth. A diagnosis of chronic localized interspinal ligamentitis was made and supported by the temporary relief of pain when the affected ligament was injected with 15 to 20 c.c. of 1 per cent solution of procaine. Operative removal of the affected tissue gave complete relief; the ligament showed chiefly degenerative changes with some nests of inflammatory cells, mostly lymphocytes. Kleinberg[459] described acute traumatic disease of interspinous ligaments.

"The Dorsolumbar Syndrome": "First Lumbar Nerve Neuralgia." A "new syndrome" was reported, called the "dorsolumbar syndrome" by Judovich and Bates, "first lumbar nerve neuralgia" by Tarsy, "causalgia of the twelfth dorsal and first lumbar nerves" by Hudson and Hettesheimer. Studies of Judovich and Bates indicated that the distribution of the twelfth dorsal and first lumbar nerves is much wider than supposed and overlaps lumbosacral and sacro-iliac regions. For certain anatomic reasons the nerves are frequently irritated at the dorsolumbar joint; a common and charac-

teristic backache results with tenderness and pain along the distribution of affected nerves. In cases of Hudson and Hettesheimer unilateral pain extended over the lower back, iliac crest or midlumbar region with hyperesthesia of skin supplied by the twelfth dorsal and first lumbar nerves. Pain and tenderness were referred anteriorly over the abdomen [434] and in some cases led to abdominal operations. Rapid relief was afforded by perineural injections,[434] or by injections of 1 per cent solution of procaine or of eucupine in oil which presumably broke up adhesions and separated fascial spaces.[753] Others [413] recommended removal of foci, correction of pelvic tilt with an elevated heel on the abducted side, and exercise to strengthen the abdominal and weaken the sacrospinalis muscles.

In some of Hudson's cases backache was minor, but abdominal pain was "intractable"—burning, boring or aching pain in either lower quadrant, aggravated by motion; it wakened patients at night and was relieved by sitting up. Pain was elicited by pressure upward over the eleventh and twelfth ribs and over the transverse processes of the eleventh and twelfth dorsal and first lumbar vertebrae. Unrelieved by abdominal explorations, the pain was relieved within two hours to two weeks by paravertebral sympathetic block with procaine; in some cases alcohol injections gave relief for a year but transient alcoholic neuritis sometimes resulted.

Backache from Tight Fascia Lata and Iliotibial Band. The syndrome was again described and indications for conservative or surgical treatment were outlined. Ober's sign is not always positive even when the iliotibial fascia is tense.[339] Fasciotomy gave good results in 45 per cent of Heyman's 12 cases, in 70 per cent of Logue's 10 cases, in 75 per cent of Smith's [701] cases, in 90 per cent of Green and Gondy's 20 cases. Fasciotomy was done by Nutter in 45 cases with success in 70 per cent of the 35 cases of sciatica with backache, in 67 per cent of three cases of sciatica without backache, in 43 per cent of seven cases of low back pain without sciatica. Fasciotomy was not satisfactory to Mumford and Reynolds. Several patients unrelieved by fasciotomy for presumed tight fascia lata were later relieved when Bradford and Spurling removed herniated disks. A "successful" conservative method was reported by Ilfeld—a new method of strapping thigh and back; of 11 patients so treated five obtained "excellent," six satisfactory results.

Sacro-iliac Backache and Sciatica from Lesions of the Pyriformis Muscle. Smith [701] did not advocate cutting the pyriformis for this supposed condition.

Backache from Developmental Anomalies. According to Dittrich spina bifida occulta is often associated with intraspinal pathologic changes, masses of fibro-adipose tissue overlying the dural sac and sacral nerve roots with fibrous cords extending between the ventral surfaces of the laminae and the dura or nerve roots. Mechanical irritation of nerves, muscle tenderness in lower back and legs, and absent or diminished knee and ankle jerks result. Laminectomy and removal of abnormal tissue was done in seven cases of "muscular rheumatism" with spina bifida; in all relief was complete. Craig

and Walsh warned that developmental anomalies are often benign and not the cause of the backache; they were frequent among 300 cases of backache relieved only by removal of protruded intervertebral disks.

Spondylolisthesis. Anterior spondylolisthesis affected five of 75 cadavers.[400] Many cases are symptomless and need no treatment.[457] Current writers[409, 439, 457, 459, 472, 550] regarded the condition as a developmental defect made symptomatic by trauma. In Kark's case, trauma alone produced the condition. A child 18 months old with the condition was mentioned.[457, 459] Conservative therapy was usually advised: rest in bed, then temporary support with belt, plaster corset or brace,[457] reduction of the deformity by applying slings[439] and traction.[472] For intractable cases fusion was recommended. George's results were: of 50 patients treated conservatively only 18 per cent obtained complete relief; 20 per cent partial relief, the rest no relief; of 91 patients treated by Hibb's fusion 81 per cent obtained complete relief. But conservative therapy was successful in "at least 75 per cent" of the cases of Krusen and Basom.

Reverse Spondylolisthesis. Horwitz[400] noted posterior displacements of from ⅛ to ¼ of an inch in nine of 75 cadavers studied.

Prespondylolisthesis: "Spondylolysis." Kleinberg[457, 460] defined this condition as the existence of a congenital laminar defect in a lower lumbar vertebra or on one or both pedicles of the affected vertebrae, separating the articular facets by a distinct gap, a condition predisposing to future spondylolisthesis. Low back pain with or without sciatica may or may not result. George reported 42 cases of "spondylolysis."

The Facet Syndrome: Arthritis of Facets. No new data were reported.

Coccydynia. This may result from spasm of levator ani, coccygeus or pyriformis muscles, and may produce not only coccygeal, but also sciatic or supragluteal, pain. Krusen and Basom recommended heat and internal (intra-rectal) massage after the method of Thiele, 1937 (technic given).

Diseases of Intervertebral Disks. Lesions of disks, not necessarily protrusions, were considered by some[43] the commonest single cause of low back pain with sciatica. Various lesions were again discussed: senile degeneration, lesions from trauma, spinal puncture needling, infections, calcification of disks, healing after injury, and those producing adolescent and senile kyphosis.[651] The anatomy and physiology of disks and related structures were described, also lesions of disks found in cadavers.[233, 400]

1. Senile Fragmentation. Degenerative changes in disks from aging and wear and tear may produce kyphosis not only in the elderly, but in young persons with congenital weakness of cartilage plates.[233] Among 75 persons, aged 45 to 80 years at time of death, narrowed disks with fibrillation of fibrocartilage and dehydration of nucleus pulposus were found between the fifth lumbar and first sacral vertebra in 50, between other lumbar vertebrae less often.[400]

2. Ruptured Intervertebral Disks. So "popular" is this subject that it

comprised a third (35 papers) of all current reports on backache under review; most noteworthy were those of Bradford and Spurling, Barr, Craig and Walsh, Fincher, and Love. In 6 per cent of 50 cadavers Batts noted anterior protrusions of disks, in 20 per cent protrusions into vertebral bodies, in 16 per cent posterior protrusions. Frank posterior protrusions were found by Horwitz[400] in only four of 75 cadavers. The relative importance of ruptured posteriorly protruding disks as a cause of backache and sciatica has not yet been established. Some consider them the commonest cause of low back pain with sciatica; thus of Adson's 60 patients who underwent operations for that complaint 35 had herniated disks. Posterior protrusions of disks complicated 42 of Olin's 50 cases of fractured vertebrae. A dozen papers detailed the clinical features of over 600 cases of protruded disks proved at operation to be the cause of low back pain generally with sciatica. Some of the 600 cases were continuing series partly reported previously: thus 300 cases were reported from the Mayo Clinic,[201, 499, 793] but it was emphasized that this large number accepted for such surgical treatment were only about 2 per cent of 13,000 cases of low back pain with sciatica seen by orthopedists of that Clinic during the same three year period.[201, 378, 499]

Etiology. A history of trauma was found as follows: recent trauma in 37[201] to 50 per cent,[45] remote trauma in 22[201] to 30 per cent,[45] no known trauma in 17,[90] 20[45] and 41 per cent[201] of cases. As in previous series the greatest frequency of the protrusions was between the fourth and fifth lumbar or the lumbosacral bodies.[11, 45, 90, 93, 201, 499, 793] Among the 300 cases of Craig and Walsh lesions were lumbar in 285, cervical or thoracic in only 15. In the Mayo Clinic series protrusions were multiple in about 10 per cent.[201, 499, 500] From 70[93] to 75 per cent[90, 201] of the patients were men.

Symptoms. Many herniated disks produce no symptoms but are obvious only roentgenographically; such require no treatment. Symptoms when present consist of root pains generally involving lumbar, sacral and sciatic regions. They are *not pathognomonic* but simulate those produced by several syndromes. Sciatica was unilateral in 85 per cent, bilateral in 15 per cent of one series of cases.[201] Neurologic examinations were entirely negative in 6 per cent of the series, and in 15 per cent more they were negative except for a positive Lasègue's sign and/or sciatica.[201] But usually a characteristic clinical syndrome is present. Reflexes may be normal[11, 480] but usually are not.[720, 721, 722] The Achilles reflex was abnormal in 43 to 50 per cent of cases.[45, 93] In all Barr's cases positive Lasègue's signs were present, in 90 per cent reversal of lumbar curve, in 60 per cent sciatic scoliosis, in 35 per cent sensory changes in extremities, in 15 per cent motor changes (weakness, palsy), in 5 per cent sphincter disturbances, in 50 per cent local tenderness over the affected lumbar spinous processes (also in 50 per cent of Fincher's cases), in 40 per cent root pains on coughing, sneezing or jugular compression. Other analyses of symptoms were given.[93, 201] In one group only 5 per cent of patients had sciatica *without* low back pain.[201]

Among Barr's cases symptoms were constant in 60 per cent, intermittent in 40 per cent (they were intermittent in 81 per cent of the cases of Craig and Walsh). In one case[20] of protruded disk a meningitic cyst (circumscribed arachnoiditis) was produced by mechanical irritation from the disk protrusion; in some cases pain may be caused, not by the disk, but by associated inflammatory processes.

Diagnosis. Ordinary spinal roentgenograms in cases of protruded disks may or may not be helpful; they often reveal what is *not* the cause of pain, e.g., osteophytes, developmental defects, narrowed intervertebral spaces without protrusions.[90, 93]

But narrowed spaces corresponding to the neurologic level of pain are suggestive evidence of a damaged disk with protrusion.[11, 45, 500] Spinal fluid protein is usually increased, but is sometimes normal[43, 90, 480]; it was under 40 mg. in from 11 to 25 per cent of cases,[11, 93] over 40 mg. in 66 to 85 per cent of cases.[11, 45, 201] When spinal fluid protein is normal, the reversed Queckenstedt test is a valuable sign[11] and should be positive before spinograms are done.

Air myelography (pneumospinograms, airograms) is much less dangerous than myelography with lipiodol, and was preferred by some[161, 272]; if results therewith were doubtful, spinograms with lipiodol were made. The technic of air myelography was described.[136, 201] Most physicians agreed that air myelograms were satisfactory in cases of complete spinal block but were generally quite inferior to those with lipiodol and not to be relied on.[106, 136, 218, 546, 643, 675, 697, 701] The technic of spinograms with lipiodol was described[90, 136] and the diagnosis was predicted accurately in 92 per cent of 210 cases. Although some physicians insisted that 2 c.c. of lipiodol were enough,[93, 454] the majority considered 5 c.c. necessary for accuracy[11, 45, 136, 500, 651] and noted no notable reactions.[45, 272, 697] Bosworth and Hare noted fresh intradural adhesions two or three days after injection of lipiodol; Mumford and Reynolds noted severe reactions in "at least half" of their 13 cases in which lipiodol was used. All writers agreed that such spinograms should never be made indiscriminately, but only after careful preliminary general, neurologic and orthopedic examinations, and the oil should be removed surgically. Because of objections to such spinograms some physicians, on the basis of increased clinical experience with the characteristic findings, performed laminectomy without the use of lipiodol injections.[501, 675]

In summary, patients with recurring low back pain and sciatica with or without a definite history of trauma, with exaggerated spinal flexion or torsion, a positive Kernig or Lasègue's sign, diminished Achilles reflexes and an increased protein in the spinal fluid should be suspected of having a protruded disk and myelograms should be made after injection of air or lipiodol.[11]

Pathology. The extruded material does not represent chondromas, as was once believed, but consists of all the parts normally found in unprotruded disks. The tissues are altered: present are degeneration of cartilage cells (more often than of fibrils), proliferation of fibrous tissue and edema of protruded tissues. Variability in the edema may account for the intermittency of symptoms.[224]

Treatment. Facetectomy alone was considered inadequate.[200, 201] Surgical technic for laminectomy and removal of the protruded disk was described.[11, 45, 200, 272, 499, 500, 720] The radiopaque oil should be removed: a special method for this was suggested.[580] The hypertrophied ligamenta flava so often found should also be removed. Laminectomy should not be done until conservative therapy (rest in bed, heat, traction) has failed and the sciatica has become recurrent, because conservative measures may reduce small protrusions.[11, 720] Manipulation may relieve pain by stretching and paralyzing involved nerve roots but is inadvisable because it may precipitate paraplegia.[45] Some physicians[45, 106, 701] advocated bone graft at the conclusion of laminectomy; others with large experience considered it rarely if ever necessary.[11, 378, 675]

Results of Treatment. Immediate results of laminectomy were usually excellent. Almost every one of Barr's 83 patients noted immediate relief; there were three failures, two deaths. Of 18 other patients, 15 were relieved; one died.[90] Among 35 cases of Bradford and Spurling results were excellent in 26, good in seven; there were two deaths, one postoperatively, one late. Pain recurred in one case until arachnoidal adhesions were removed. Among Fincher's 50 cases, relief was complete in 80 per cent, partial in 10 per cent, not obtained in 10 per cent; there were no deaths. The largest series was that of the Mayo Clinic: results among 300 cases were generally excellent; one patient had a nonfatal postoperative hemorrhage; only one of the 300 patients died (infected wound and bronchopneumonia).[201, 499, 500, 501] It is too early to evaluate results finally or to determine the number of late recurrences.

Only one writer jarred the harmony of these reports. Pappworth caustically criticized the members of one Boston group, pointing out apparent contradictions and discrepancies in their various papers. He suggested that the rest in bed and not the laminectomy may have been the cause of relief in many cases, and advocated "a closed season" on the writing of papers on this subject until a more judicious appraisal of late results can be made. He was unable to believe that the symptoms were due chiefly to the protruded material but suggested that many of the protrusions were incidental findings.

[The best answer to this criticism is the insistence of the writers that most of the patients treated surgically had failed to respond to prolonged conservative and "nonsurgical" treatments including rest in bed, and one orthopedist[378] agreed that results from laminectomy are far superior to those attained by older surgical or nonsurgical orthopedic measures.—Ed.]

Backache and Sciatica from Hypertrophied Ligamenta Flava. Hypertrophy of these ligaments often accompanies ruptured disks: the trauma which ruptures the disk also tears the ligamenta flava which hypertrophy during healing.[11, 480] Hypertrophied ligamenta flava were found by Craig and Walsh in 155 of their last 175 cases of protruded disks. Such hypertrophy often occurs alone, perhaps from localized extradural hemorrhage producing fibrosis and thickening.[45] Symptoms are usually low back pain with sciatica; signs resemble those from ruptured disks.[546, 766] In one case[93] there was no pain, but trophic ulcer of heel, incontinence of urine and feces,

and saddle anesthesia were noted. Among 75 cadavers Horwitz [400] found no pressure on caudal nerve roots from hypertrophied ligamenta flava. Treatment involves laminectomy and removal of the hypertrophied disks.[161] Of 13 cases of Bradford and Spurling late results were: complete relief in eight, postoperative death in one, much relief but slight residual pain in four cases.

Backache from Senile Osteoporosis. Elderly persons, usually females, often present stiff, tender spines with marked osteoporosis, reduction in size of vertebral bodies, and increased dorsal curve. The cause is unknown; no known chemical abnormality is present in blood.[233, 457] Recommended were complete rest from weight bearing for two to three months, then physical therapy and a brace.

[Albright and colleagues called this condition "post-menopausal osteoporosis" and recommended estrin therapy to produce a positive calcium balance.—Ed.]

Miscellaneous Conditions of the Spine. 1. Malignancy. Among 60 patients operated upon for low back pain with sciatica three had spinal malignancy.[93] In one case sciatica was caused by prostatic carcinoma; therefore, rectal examinations should be done in all cases of sciatica.[762] For intractable spinal malignancy Love [499] advised sedatives and injections of alcohol into the subarachnoid space.

2. Rickets of the Spinal Column. Roentgenologic features were described (Oppenheimer).

Myofasciitis of the Back: Lumbago. Acute lumbago or lumbar myofasciitis supposedly is caused usually by sprains, but of this there is often no pathologic proof; hence Makaroff blamed acute vasospastic disorders related, perhaps, to small emboli from distant foci [no proof given.—Ed.]. According to Albee and Campos myofasciitis, a "toxic inflammation or metabolic change of muscles and their associated fasciae," is the commonest cause of low back pain. Among 1188 cases trauma was a factor in only 25 per cent. They blamed the condition on infected foci, constipation with an "elevated histamine index of the stools," uric acid retention, nervous strain or vitamin deficiency and allergy [or what have you! No proof for these ideas was given.—Ed.].

The pathologic basis of lumbago is unknown; in most cases none can be demonstrated, but in two of Kleinberg's [457] cases biopsies revealed inflammation of gluteus medius muscle, in three cases hyaline degeneration.[459] According to Albee and Campos subcutaneous nodules contain a gelatinous substance infiltrated with leukocytes, sometimes round cells [no specimens shown.—Ed.].

Albee and Campos again described the "myofasciitis (leg-raising) test." Although roentgenograms were "negative," Albee and Campos considered myofasciitis a "pre-arthritic condition" which, neglected, may lead to arthritis. Despite the uncertain pathology of the condition Heyman stated that the lumbar fascia is often thick and taut: the most important diagnostic

sign was localized tenderness at or near the posterior superior spine plus painful forward bending and straight leg-raising.

Treatment. Conservative measures included rest and physical therapy. Others recommended fasciotomy with or without muscle stripping.[384, 457] According to Gorrell lumbago "can often be relieved in five minutes, cured in an hour" by injecting 10 to 25 c.c. nupercaine solution into "trigger points" and then prescribing immediate active *use,* not rest, of muscles; he cited 13 cases of relief from one or two injections. Nupercaine often produced transient vertigo; the effect of procaine was too transient.

Postural Backache. Many writers included this under "lumbosacral strain," others[457, 726] considered it a separate entity. Faulty posture may produce low back pain with a true sciatic endoneuritis or perineuritis. For patients not relieved by conservative means (proper shoes, postural exercises) epidural endosacral and endoneural injections of procaine, or nerve-stretching were used.[726]

Lumbosacral and Sacro-Iliac Backache and Strain. Under this vague heading physicians described and treated many cases of acute or chronic low back pain. In 96 per cent of the cases of Mumford and Reynolds caused by "effort strain from indirect trauma," relief occurred within one to four weeks from "almost any treatment." Recommended were good adhesive strapping, rest in bed with knees flexed, after five days removal of adhesive tape and use of physical therapy. Epidural injections, manipulations, casts and corsets had not given relief.

"Lumbosacral sprain." Goff described his technic for finding the "trigger point," the chief site of strain, and curing it by intramuscular, or if necessary by epidural injections of procaine.

"Sacro-iliac sprain." This is rare according to some,[420, 701] common according to others. It can be demonstrated unmistakably in roentgenograms according to Chamberlain; roentgenograms may show hazy sacro-iliac joints from acute effusions within 24 hours after injury[459] and such sprains are the commonest cause of "industrial backaches." Recommended were long protection of the back with plaster jackets, later corsets, physical therapy and graded exercises; for stubborn cases manipulation without anesthesia (technic given)[414] or arthrodesis.[459]

Unclassified "Low Back Pain" with or without Sciatica. Manipulation without anesthesia was recommended.[414, 432] [The technic was given; apparently the presence of sprain was implied.—Ed.] Others used local injections of eucupine in oil,[420] postural exercises and supports, rarely fusion.[427]

Additional Comments on the Treatment of "Backache and Sciatica." In 90 per cent of cases in which no more specific diagnosis can be made, conservative measures give relief; in 10 per cent or less fusion is needed.[94, 577, 759] Conservative measures included rest, traction, hot applications, later braces or plaster shells, spinal massage, postural exercises.[43, 166, 370, 630, 759] Local or regional injections of procaine or eucupine in oil were also used.[290, 730, 753]

Sciatica: Additional Comments. Comments on the classic of Cotunnius were made.[28] Harris classified sciatica thus: (1) high sciatica from lesions near intervertebral foramina around the fourth and fifth lumbar nerves caused by osteo-arthritis, septic inflammation or rheumatic disease (e.g., fibrositic sciatic perineuritis); Achilles jerks are normal, the patient often leans away from the affected side; (2) low sciatica caused by lesions near the sciatic notch, a true "toxic neuritis" from lead, arsenic, diabetes, an infective neuritis from infected foci, a traumatic neuritis or one from direct

chill to the buttock; the Achilles jerk is often lost and the patient leans toward the affected side. According to Burt there is (1) root or high sciatica, (2) trunk (low or true) sciatica, and (3) referred sciatica from arthritis, bursitis, fibrositis. Of his 140 cases of "rheumatic sciatica" 35.5 per cent were of the root, 17 per cent trunk and 45.5 per cent referred type. [This equals 98 per cent.—Ed.]. A pathologic specimen of trunk sciatica (microphotographs) showed exudative swelling and thickening of the epineurium, engorgement of blood vessels and perivascular lymphocytic exudate; organization of exudate leads to formation of adhesions. Wagoner reported cases of sciatica from fibrous adhesions about the nerve, relieved completely by surgical removal of the constricting fibrous tissue. The causes and treatment of sciatic scoliosis were discussed.[457, 459] The intrathecal use of alcohol for sciatica is dangerous; it should be employed only in cases of intractable pain from malignancy, but in such cases chordotomy was preferred.[457, 459] Bilateral sciatica is more serious than unilateral sciatica and generally indicates intraspinal lesion, tumor or malignancy.[101] For trunk sciatica rest, heat, injections of saline into and around the sciatic sheath and, if necessary, nerve stretching under anesthesia were recommended; massage was condemned.[127, 367, 657] If acute sciatica fails to improve under such treatment or pain increases, an intraspinal lesion requiring laminectomy is usually present.[200]

Atrophic (Ankylosing) Spondylitis

Clinical Data. Data on two new series of cases were reported.[285, 742] Sex incidence in Swaim's 106 cases was 84 males, 22 females; the ratio may be as high as 20 males to one female.[51] In over 80 per cent of Forestier's cases the condition had escaped diagnosis during its first three years when only vague pains of lower back or chest were present. Small joints of only five of Swaim's 84 males were affected.

Laboratory Data. Sedimentation rates are usually high, sometimes higher than in peripheral atrophic arthritis.[310]

Roentgenograms. For early diagnosis it is most important to know that the earliest roentgenographic changes almost always affect sacro-iliac joints,[151, 285, 669, 742] but projections from several angles may be required to demonstrate sacro-iliac and intervertebral changes. Sacro-iliac joints were not involved in only two of Forestier's 153 cases. He described the various roentgenographic stages of the "sacro-ileitis": first stage, periarticular marginal decalcification; second stage, pyknotic formation, giving a mottled appearance, with both decalcification and hypercalcification; third or terminal stage, total fusion with fibrillary ossification and regions of osteosclerosis. When only a few small regions of intervertebral ligamentous calcification are present, they may be confused with osteophytes. According to Forestier the former, "syndesmophytes," can be differentiated easily from osteophytes from the beginning: the former appear as a wooly shadow in the inter-

vertebral space; in a few months a rather clear-cut, dense, linear area of calcification without a cortex appears which looks like a thin or thick comma on the vertebral body; osteophytes have a much thicker base, are covered with a cortex arising from that of the vertebral body, and a structure of cancellous bone like the vertebral body itself.

Etiology. In 60 per cent of Forestier's cases genito-urinary infections, not necessarily specific, were present; perhaps toxic products from the male genito-urinary tract spread via pelvic lymphatics to spine; in women the lymphatic spread from pelvic organs does not approach the iliac joints.[34]

Treatment. The usual medical and orthopedic remedies were reviewed.[447] Such a program (hyperextension in bed, use of plaster half-shells, physical therapy, corrective exercises, then braces) gave results unsatisfactory to Swaim: in 35 of 45 cases in which this treatment was used affected vertebrae fused completely in 35, in 31 posture remained poor, in 21 motion of the hips was lost; death from pulmonary infections occurred in nine cases. A superior plan was evolved: preliminary correction of spinal deformity by hyperextension in bed for two weeks, then the application of a plaster jacket " for early, continuous and adequate immobilization." Jackets were left on for weeks, replaced by new ones as posture improved; they were worn by 62 patients for from months to nine years. Muscle spasm and pain were rapidly relieved, sleep improved markedly despite the jacket, deformities were prevented or improved notably, expansion of the chest and weight increased. No new hip trouble occurred and vertebral bridging was definitely retarded.

Chrysotherapy in conjunction with intramuscular or intravenous injections of thorium-X or radon was highly recommended by Forestier: 80 per cent of 25 patients became symptom free within two years. Bach also recommended chrysotherapy but it disappointed others [447, 452] as did fever therapy.[102] Kersley advocated deep roentgen therapy to relieve sacro-iliac pain. But neither deep nor short wave length roentgen-rays should be used " under any circumstances " according to Scott who extolled the virtues of widefield irradiation which sometimes gave " spectacular results." Others [250] did not share Scott's enthusiasm.

Hypertrophic Spondylitis (Osteo-Arthritica)

Clinical Data. Marginal vertebral osteophytes have too long masqueraded as hypertrophic spondylitis; when present they may not be the cause of a patient's pain, according to Chamberlain who preferred Kienbock's term " trophostatic osteoarthrosis." Hartsock described headaches from cervical hypertrophic spondylitis: apparently first occipital, then temporal, they really originated in the cervical region; muscular tenderness at the trapezius attachment to the skull was important in diagnosis; they were precipitated by damp and drafts, aggravated by flexion of neck and lasted longer than attacks of migraine.

Etiology. Spinal hypertrophic arthritis is now generally regarded as merely a phase of "discogenetic disease": age and trauma produce degeneration of disks (not necessarily with herniation), partial luxation of vertebral bodies, narrowing of intervertebral foramina with production of root pains, and irritation of marginal bone of vertebral bodies with osteophyte formation.[43, 233, 579, 651] The importance of industrial trauma as a provoking and aggravating factor of hypertrophic spondylitis was stressed.[286, 295, 512, 584, 596] When an Ohio worker over 40 years old with symptomless, perhaps unsuspected, hypertrophic spondylitis falls down, the cost to his employer is likely to be about $3000, according to Papurt. Such cases are costly to industry, but industry must absorb the cost. Routine roentgenograms of elderly workers are not worth the cost and, if done, would result in an "employment junk heap."

Treatment. One writer [150] considered removal of foci useful. In cases precipitated by industrial trauma prompt rest in bed is better than frequent traumatizing trips to a physical therapist's office.[512] [Solution: have the physical therapist go to the patient's bedside.—Ed.] The associated fibrositis requires heat and massage but not exercises [447]; manipulation may afford relief.[386] Patients with cervical osteo-arthritis should wear woolen neck protectors to avoid drafts, especially at night.[369] Also recommended were head sling, soft rubber heels to prevent jarring when walking, and cervical traction by the method of Hanflig (1936).[472] Of 38 patients treated by such traction all obtained some relief.[758]

Gout and Gouty Arthritis

The number of papers on gout was fewer in 1939 than in 1938. The informative article of Brøchner-Mortensen [100] should interest all students of the disease. It gave a detailed analysis of 30 cases with careful studies on excretion of uric acid. Other papers added singularly little to our knowledge of the condition. Some [128] complained: "Although a whole day was devoted to gout at the recent International Congress on Rheumatic Diseases no startlingly new contributions emerged."

Incidence. The usual controversy about the relative frequency or infrequency of gout prevailed. According to Tolstoi, "The problem is not of tremendous importance in this country as statistics have shown that gout is a relatively rare disease." He quoted statistics to show that the current incidence of gout does not compare with that many years ago.

Futcher observed 124 cases of gout among 53,012 medical admissions to Johns Hopkins Hospital. Between 1903 and 1916 gout was diagnosed only 42 times among 298,500 patients at the Massachusetts General Hospital (Pratt, 1923). At the New York Hospital gout was diagnosed only eight times among 177,000 patients in five years. Gudzent and Holzman found 76 cases among 32,089 postmortem examinations. According to Brøchner-Mortensen [100] the incidence of gout has diminished since 1914. He attributed recent "increases" in incidence to an "unjustified" broadening of the diagnostic criteria. Other reports [789] supported Hench's claim that "it is the suspicion

of gout, not the disease, which has disappeared." Thus among 2500 patients, Wade observed five with gout, an incidence of 0.2 per cent.

[Some find it difficult to explain variations in statistics on the incidence of gout. Those who believe that the diagnostic criteria are reasonably well standardized must conclude that the incidence varies notably in different countries, even in different parts of the same country. The social level of the clinical material under observation may be an important determining factor; many more cases of gout are seen in private practice than in the large arthritis clinics of the great metropolitan hospitals; others believe that the supposed variations in incidence simply reflect different diagnostic standards for gout in different localities.—Ed.]

Factors Governing Incidence: 1. Heredity. Heredity is generally considered a contributing factor. But Brøchner-Mortensen found a hereditary factor in only one of his 30 cases. After evaluating such factors as alcohol, overeating, lack of exercise, "animal diet," severe study, mental anxiety and exposure to lead, Tolstoi concluded that "the only positive evidence related to the causation of gout is heredity."

2. Sex. The usual marked preponderance of males was present in the one series [100] reported which included 29 males and one female.

3. Age. The same series gave the age of onset of the first attack as follows: 10 to 20 years in one case; 20 to 30 in two; 30 to 40 in seven; 40 to 50 in 10; 50 to 60 in five; 60 to 70 in four; doubtful in one. The patients' average age at the first attack was 45 years.

4. Dietary Habits. Only a few abstainers with gout were noted by Brøchner-Mortensen. Eighteen of the 30 consumed much alcohol, especially beer. "Diet may play some rôle but the character of the [offending] diet has not been determined." [771]

5. Geography and Race. The disease is unknown in China, Japan and the tropics; Russians, Poles, Swedes and Danes are comparatively immune.[771]

Clinical Data: 1. Provocatives. Further comments on the provocative effect of diets high in fat, low in carbohydrates and protein were made by Lockie. Such a diet provoked attacks of acute gouty arthritis in five of Lockie's cases, nine out of the 10 times it was used. But Brøchner-Mortensen was unable thereby to provoke attacks in four cases and concluded that Lockie's test was of no diagnostic value.

Certain foods low in purines (e.g., strawberries) may provoke attacks.[410] The provocative effect of salyrgan diuresis on five gouty patients was again [6] reported by Price.

2. Tophi. Tophi, verified by the murexid test, were noted in seven of the 30 cases of Brøchner-Mortensen; roentgenographic defects resembling tophi were present in 13 other cases.

3. Unusual Clinical Features. A case of erythremia with gout and subleukemic myelosis [624] and one of gout producing ankylosis of multiple joints were reported.[144] A patient who may have had both gouty and tuberculous arthritis was noted.[512]

Irregular Gout (Atypical Gout, Retrocedent Gout). Brøchner-Mortensen advised caution in diagnosing gout in the absence of acute attacks, tophi and hyperuricemia. But Edgecombe defended the idea of "irregular gout" which McKay attributed to the presence of allergy and gout.

According to McKay, allergy and gout, combined in an individual, may give rise to a distinct variety of gout not previously recognized. Irregular gout occurs among those who possess a gouty diathesis plus an allergic constitution. The following symptoms were supposedly due to "allergy-gout": cutaneous eruptions, nervous mani-

festations, diseases of the eye and eyelid, nasal affections, "run-away heart," and certain gastrointestinal and bronchial symptoms. The diagnosis depends on the demonstration of both gout and allergy. The three characteristics of gout, excess uric acid, deposition of crystals of sodium urate and recurrent attacks of acute arthritis, occur, but in allergy-gout the actual deposition of sodium urate is rare.

[This long, rather verbose article was based largely on experiences of the author and members of his family. The data seemed unconvincing to us.—.Ed.]

Laboratory Data: 1. Relation of Blood Uric Acid to Gout. All methods of determining the uric acid content of blood depend on some modification of Folin's colorimetric methods; they all possess certain fundamental errors, according to Brøchner-Mortensen [99] who described his own method, based on the reduction of potassium ferricyanide. [Methods involving the use of this reagent have been considered inaccurate by some physicians.—Ed.] Determinations were made on serum. Brøchner-Mortensen's method gave the following results for 32 normal persons: for males, 5.4 to 8.8 mg. per cent; for females, 4.4 to 8.1 mg. per cent. When normal individuals were taking a purine-free diet, serum levels were about 1 mg. lower. There was no relation to age, stature and weight. The upper limit of normal (serum), therefore, was taken at 9 mg. per cent for males and 8 mg. per cent for females. Hyperuricemia was present in 22 (73 per cent) of 30 cases of gout. The degree of hyperuricemia was somewhat dependent on the length of the disease. During the first two or three years increased values were infrequent but subsequently were almost constant. No constant relation was observed between acute attacks and variations in the uric acid content of the serum.

[Readers are referred also to Brøchner-Mortensen's monograph [98] on uric acid in blood and urine.—Ed.]

The same author studied the excretion of uric acid by the kidneys of 30 gouty patients: no interference with clearance of uric acid as contrasted with that of urea and of creatinine could be demonstrated; three patients had nephrosclerosis; two chronic hemorrhagic nephritis and three, slight reduction of renal function. No difference was observed in the excretion of uric acid by normal persons and gouty patients after administration of purine.

2. Serum Protein. These were slightly low in four cases of gout.[671]

[It was not stated whether the tests were done during or between attacks.—Ed.]

3. Sedimentation Rate. The sedimentation rate of erythrocytes was normal in 11 of the 30 cases of Brøchner-Mortensen, moderately increased [presumably during acute attacks—Ed.] in four and greatly increased in 15. With exceptions the rate was more or less proportional to the severity of attacks, but not with the level of blood uric acid.[310]

4. Liver Function. Various tests of liver function revealed slight insufficiency in 14 of the 30 cases of Brøchner-Mortensen. This was attributed to associated alcoholism.

Etiology. An attempt was made by Grabfield [332] to associate gouty attacks with interference of the function of renal nerves. He noted that

cinchophen increases the excretion of uric acid of intact animals but not of animals with denervated kidneys. Ergotamine in appropriate doses blocks the sympathetic impulses to the kidney. When given in a case of gout, ergotamine produced a mild attack of gouty arthritis with diuresis of chlorides and reduction in excretion of uric acid. Thus interference with impulses through renal nerves produces effects similar to those observed in gout.

[Further studies along this line will be awaited with interest.—Ed.]

Levinthal suggested that the explosive onset of classical acute gouty arthritis may be caused by an exogenous antigen which only enters the circulation occasionally, or is absorbed through a breach in intestinal epithelium before the complete cleavage and denaturation of the food antigen [no proof given—Ed.].

Treatment. Conventional treatment was reviewed.[128, 390, 449, 539, 789] The low purine, low fat, high carbohydrate diet advocated by Lockie and Hubbard (1935) was reported on favorably by Bartels. [As cinchophen was given simultaneously, it is impossible to evaluate the results.—Ed.] Massive doses of synthetic crystalline vitamin B_1 (as given by Vorhaus and Kramer) were used in nine cases by Callahan and Ingham. [As these patients received conventional treatment in addition, no conclusions can be drawn.—Ed.] Colchicine gave marked relief in Lockie's 75 cases of proved gouty arthritis but had no comparable effect in 50 cases of other forms of arthritis.

Action of Colchicine. The physiologic effects of colchicine on animal tissues were studied.[41, 121, 140, 280, 346, 371, 581, 767, 768] Its effect on gout was unexplained. Colchicine increases mitotic figures: there is doubt whether it arrests cell division in the metaphase or whether it actually stimulates mitosis.[581]

Cinchophen Toxicity

Toxic reactions from cinchophen in cases of gout or atrophic arthritis were not reported, but a patient of Coventry took cinchophen and anacin for "rheumatic fever," and nonfatal agranulocytosis (leukocytes 2600) developed.

The relationship of skin sensitivity to cinchophen toxicity was studied (Rawls, Gruskin, Ressa and Gordon). Cinchophen dissolved in blood serum was used for skin tests. In 30 of 50 cases "cinchophen toxicity" developed when 7½ grains were given three times daily for four weeks. Skin reactions were positive in 58 per cent of the entire group. Toxic reactions developed in 79 per cent of the cases in which skin reactions were positive, in only 33 per cent in which they were negative. Liver function tests gave normal results in 71 per cent of the cases in which reactions to skin tests were negative, in only 27 per cent in which they were positive. The authors concluded that such tests were of value in determining the likelihood of toxic reactions to cinchophen. [The list of symptoms used as evidence of "cinchophen toxicity" was pretty inclusive. Some patients with atrophic arthritis have some of these symptoms without having taken cinchophen.—Ed.] Winters, Peters and Crook noted that if pectin was fed to dogs that had peptic ulcers from cinchophen, healing occurred rapidly; if pectin was given concurrently with cinchophen, ulcers developed in only 11 per cent of the dogs,

whereas they developed in 100 per cent from cinchophen alone. Pregnancy and antuitrin S have little or no effect on cinchophen ulcers in dogs.[264]

[Peptic ulcer caused by cinchophen has not been reported in cases of gout.—Ed.]

The Uric Acid Problem

A method for estimating the "true uric acid concentration" of blood by means of uricase was described (Blauch and Koch [82]). Fifty samples of human blood gave an average reading of 3 mg. per cent of uric acid by old methods and only 2 mg. by the "uricase method." Approximately a third of the color produced was considered due to substances other than uric acid. The uric acid content of certain mammalian bloods was estimated by this method.[81] Since human blood does not destroy uric acid, it apparently contains no uricase. [This method should be tried in cases of unexplained high concentration of blood uric acid and in cases of gout.—Ed.] It was reported again [10] that high fat diets reduce the excretion of uric acid of normal individuals. Grabfield found that sorbitol, mannitol, sucrose, raffinose and fructose, given intravenously, strikingly increased the urinary uric acid of dogs; dextrose, xylose, maltose and galactose did not produce a measurable increase. This effect was believed to be due to the alcoholic grouping at both ends of the chain. The use of some such substance to increase the uric acid output in gout was suggested. Grabfield and Swanson noted the effect of cinchophen on excretion of uric acid in normal dogs and in dogs with unilateral denervation of the kidney. Ureters of the dogs were first exteriorized. Cinchophen decreased the volume of urine both from the normal, and from the denervated kidney. It also caused a marked increase in excretion of uric acid from both normal kidneys in dogs used as controls. After denervation of one kidney cinchophen no longer increased the excretion of uric acid from either kidney. Thus, unilateral denervation produced effects similar to bilateral denervation. The coincident administration of ergotamine and cinchophen acted like denervation.[332]

The administration of purines augments uric acid clearance by at least 50 per cent.[99] Labor of pregnancy can produce a marked increase in plasma uric acid and the longer the labor the greater the increase.[202] One normal woman had a concentration of 10.4 mg. per cent of blood uric acid during labor. This returned to normal in a few days. According to Cadden and Stander, the increased blood uric acid in eclampsia is not due to decreased excretion but to impaired destruction of uric acid in the liver: five cases of eclampsia were studied: in all excretion of uric acid was normal. A review of the literature on urinary lithiasis with specific reference to uric acid stones was published.[622]

Psoriatic Arthritis

Incidence. The differentiation between true psoriatic arthritis and psoriasis with coexisting arthritis is often difficult. Arthritis of some sort appeared at some time or other during psoriasis in 25 per cent of Madden's

44 cases, in 8 per cent of Tobias' cases. The reported incidence of "psoriatic arthritis" varies from 1 to 7 per cent of cases of psoriasis.[258] But many such cases do not represent true psoriatic arthritis; the incidence of the latter is more nearly 1 per cent of patients with cutaneous psoriasis, according to Epstein. Of Madden's 11 cases of psoriasis and arthritis, the arthritis did not immediately precede, accompany or follow the psoriasis in any case, but in one case there were simultaneous exacerbations and remissions of both the psoriasis and the arthritis. [Probably most of these were not cases of "true" psoriatic arthritis.—Ed.] About 200 cases of psoriatic arthritis have been reported in the literature.[258]

Definition. Psoriatic arthritis was defined by Epstein as "a form of atrophic arthritis associated with psoriasis and exhibiting a *reasonable amount* of synchronous activity, as evidenced by remissions and relapses, in the articular and cutaneous manifestations." Tobias considered the common type one with "primary involvement of the terminal phalanges."

Clinical Features. Details of 33 "typical cases" were given by Epstein, who differentiated the disease from keratosis blennorrhagica.

[Since Epstein did not see these cases but merely collected them from the literature his study is somewhat lacking in authority since he had to rely on the questionable diagnostic accuracy of others.—Ed.]

Fifty-two per cent of the patients were females. The disease may occur at any age but the greatest incidence occurred between the ages of 20 and 40 years. A mother and her daughter both had the disease. Reputedly heredity plays a rôle in 25 per cent of cases. In 18 per cent psoriatic arthritis and pustular psoriasis coexisted. The skin lesion generally appeared (average 6.6 years) long before joints became involved. When joints are affected, the skin lesion has generally become generalized; it was generalized in 79 per cent of these 33 cases. Joints were affected in the following percentage of the cases: hands in 97, knees in 69, feet in 61, ankles in 44, elbows and wrists each in 39, shoulders in 30, hips and "spine" each in 15, and sacro-iliac joints in three. The arthritis is basically of the atrophic variety, tends to be chronic and deforming and may cause ankylosis. Small joints of hands are generally affected first, larger joints later. Patients with psoriatic arthritis are usually ambulatory except during acute relapses. Involvement of large joints may later confine the patient to bed; ankylosis of knees, ankles and other large joints may cause crippling. Nails of fingers or toes were affected in 79 per cent of the 33 cases. Pitting, longitudinal or crosswise ridging, and heaping up of amorphous material beneath nails were characteristic. The disease of joints and skin persists through life with frequent relapses and remissions.

Etiology. Psoriasis is believed by some to result from a disturbed fat metabolism and to be associated often with hypercholesterolemia. According to some, relapses in joints are associated with hyolipemia (Weissenback, Martineau and Bowens, 1938). But hypercholesteremia was usually absent in Madden's cases of psoriasis, and cholesterol tolerance tests were of no value in forecasting results of low fat diets.

Data on Psoriasis. Among Madden's 44 cases of psoriasis, remissions were ascribed to pregnancy, rheumatic fever and arsenic pills; exacerbations

to many factors including cholelithiasis. Thirty pregnancies affected eight psoriatic patients: in 14 pregnancies "the psoriasis almost disappeared"; lesions usually began to disappear at the end of the first trimester and the disease steadily improved during the rest of pregnancy. Whatever the effect of the first pregnancy on the psoriasis, succeeding pregnancies produced a similar effect.

[The effect of pregnancy on the arthritis was not stated.—Ed.]

Treatment. The effects of fever therapy [258] and of salts of manganese [757] on joints were "disappointing." Treatments for the skin lesions were reviewed.[298, 770] Of Madden's 22 patients given low fat diets (20 gm. daily), 68 per cent noted improvement in the skin lesions, but results may have been due to a general realinement of metabolism and tissue function rather than to correction of disturbed fat metabolism. The use of lipocaic (a neutral, alcoholic, fat free extract of pancreas) improved four of six patients with psoriasis.[736]

Hemophilic Arthritis

In current papers on hemophilia joint changes were considered in only one: Newcomer presented a partial review of the literature and reported the clinical and radiologic features of hemophilic arthritis. In about 80 per cent or more of cases of hemophilia joint symptoms develop sooner or later for which operation is often mistakenly instituted. Intra-articular hemorrhage occurs and may cause destruction of cartilage. Degenerative joint changes and destruction of cartilage produce a "typical hypertrophic joint." Occasionally the changes are more atrophic than hypertrophic in type. Treatment of hemophilia with newer substances was described.[270, 409]

Allergic Arthritis

The small number of articles which appeared under this heading is a hopeful sign that internists and rheumatologists are becoming more critical. Only 2 articles dealing specifically with the subject appeared. Boemer presented nine cases of a triad, infection, arthritis, allergy, as a clinical entity. [The evidence was rather unconvincing.—Ed.] Wooton in a speculative mood, attempted to analyze food reactions of persons with "hypersensitive synovia." The method of determining sensitivity was not described and no controls were included. A case of "intermittent hydrarthrosis with an allergic basis" was described by Berger [66] (see section on Intermittent hydrarthrosis). The relation of allergy to certain cases of gout was discussed by McKay (see section on Gout).

Metabolic Arthritis

This term, like allergic arthritis, is falling into disuse. No articles under this title appeared. A case of ochronosis was described by Bhatia (see section on Miscellaneous diseases of joints).

Endocrine Arthritis

Thyroid Dysfunction and Chronic Rheumatism. Some writers have blamed thyroid deficiency; others have cited thyrotoxicosis as the cause of certain cases of chronic arthritis. According to Crotti muscular and joint pains commonly develop in cases of hyperthyroidism. These are relieved by thyroidectomy but, if unrelieved, may lead to atrophic polyarthritis with contractures and general decalcification. Hyperthyroidism stimulates the parathyroids to overactivity with resultant demineralization.

[The evidence presented was unconvincing; there is still no proof that any endocrine abnormality alone can cause arthritis, but it may be an important contributing factor.—Ed.]

Menopausal Rheumatism. Our last Review discussed the rather vague concept of "menopausal rheumatism." Voight was the current sponsor of the idea that the menopause can not only produce "general rheumatic symptoms" but can affect unfavorably the course of "arthritis deformans." In a hypothetical manner Voight blamed "allergy of the climacterium" as the cause of various articular and muscular symptoms including the painful shoulder syndrome (periarthritis humeroscapularis) of typists, pianists and teachers undergoing the menopause. Cases of "menopausal arthralgia" and "climacteric arthritis" were described briefly by Ishmael and Howitt, but most American physicians doubt the existence of such entities.[757]

Joints and Parathyroids. Symptoms of hyperparathyroidism include pains in bones and joints, especially of lower extremities and spine, but true arthritis is not present. Features of the condition were reviewed.[22, 24, 146, 352, 422, 467, 534, 682]

The disease may be present mildly for some time before producing characteristic chemical and roentgenologic signs.[352] Some [568] regard scleroderma as a manifestation of hyperparathyroidism. [We do not.—Ed.] A "functional hyperparathyroidism" may occur in cases of hyperthyroidism according to Crotti. [One of us, W. B., has been unable to demonstrate this.—Ed.] In such cases muscle and joint pains and even a true "thyrotoxic chronic arthritis" may be present. In Sharpe's case of hyperparathyroidism multiple "rheumatic pains" were present. In the first case of Anspach and Clifton the child complained of pains in bones of extremities, in back and fingers, and a knee was enlarged; roentgenograms revealed epiphyseal enlargement, calcifications in tendons of knee and near an acromion bursa.

For patients who cannot or will not accept surgical treatment, roentgen therapy over parathyroids was recommended by some,[24, 352, 422, 534] but not by others.[467]

[We consider roentgen therapy useless.—Ed.]

Miscellaneous Diseases of Joints

Intermittent Hydrarthrosis. According to Berger [66] intermittent hydrarthrosis is not one disease but a manifestation of several general and

local conditions (malaria, rheumatic fever, undulant fever, lymphogranuloma venereum and other infections) [also atrophic arthritis if one is considering "symptomatic" and not "true intermittent hydrarthrosis"—Ed.]. To date 106 cases have been reported. The condition occurs with equal frequency in males and females, generally aged 20 to 45 years, and is sometimes familial. Contributory causes have been infection, endocrine disease and allergy. Some cases occur with menstruation and disappear at the menopause; pregnancy often holds attacks in abeyance. Each cycle is the same for a given person, usually eight to 13 days. Berger discussed the supposed value of endocrine products, ergotamine, vaccines, irradiation and surgical measures. In his case the condition stopped when foods to which the patient was sensitive were eliminated from the diet. These were lamb, apples, pineapples, grapefruit, peaches, tomatoes, string beans, corn, olives and grape jelly.

Synovitis. Irish and Stump reported a condition not sufficiently recognized. Improper distribution of weight due to weak feet causes villous synovitis of knees with hypertrophy and fibrosis of synovial villi and hypertrophy of subcutaneous soft tissues about the knee joint. "Correction of weak feet results in complete relief of subjective symptoms."

[We are not convinced that such an entity exists.—Ed.]

Tumors of Synovia and Joint Tissues. 1. Synovial Sarcomas. A case of popliteal synovioma was reported.[147] Our knowledge of malignant synovial tumors is scant for three reasons: (1) lack of knowledge of the nature of normal synovia; (2) rarity of cases of synovial sarcomas; (3) lack of precision in case reports. Berger [67] reviewed the entire literature and added five cases, four of which seemed to represent a distinct oncologic entity. In three cases the tumors were histologically similar, and originated in serous bursae; all recurred a few months after their surgical removal. In two cases pulmonary metastasis caused death. Proposing a new classification, Berger recognized three main types of tumors: (1) a type corresponding to benign xanthomatous giant cell tumors; (2) epitheliosarcomatous tumors; (3) polymorphous tumors. The prognosis is bad. Treatment should be prompt and radical.

2. Xanthomatous Tumors of Joints. De Santo and Wilson reviewed the 32 reported cases and added nine new ones. Data on the 41 cases were tabulated.

Xanthomas are commoner than supposed; a preoperative diagnosis has apparently never been made. Obscure, intermittent swelling, pain and hydrops of a knee, occasional locking and a movable tumor, usually medial to the patella, may be caused by xanthoma. Aspiration of dark or sanguineous fluid suggests xanthoma, and demonstration of large amounts of cholesterol is probably pathognomonic. The tumors originate in chronic, hemorrhagic, villous arthritis. The stroma cell is related to the reticulo-endothelial system and produces three types of cells: (1) foam cell, (2) giant cell, and (3) pigmented cell. De Santo and Wilson viewed the condition as related to some disturbance of lipoid metabolism. Radical excision was recommended. No malignant transformation was observed.

[Berger observed such a transformation in one case.—Ed.]

3. Hemangioma of Joints. Bennett and Cobey surveyed the literature on hemangiomas of joints and added five cases. Criteria for diagnosis and treatment were discussed. Difficulties inherent in surgical excision due to hemorrhage, and the unsatisfactory results in all save the small, pedunculated type of tumor caused the authors to institute therapy with radium (in one case) and roentgen-rays (in two cases) successfully, the first application of such therapy for this disease.

Arthritis with Coccidiosis. For a discussion of the study of Faber and his associates on the acute arthritis which may accompany coccidiosis see Erythema nodosum.

Pelvic Osteo-Arthropathy of Pregnancy. Excessive relaxation of pelvic joints during pregnancy may produce chronic backache and locomotor disturbances. Young recognized two types of trouble, involvement of (1) sacro-iliac joints alone, and (2) sacro-iliac and pubic joints. Pain occurs in these regions during pregnancy and is aggravated by walking; walking may be difficult or impossible; the gait may be waddling. Among 34 of 4512 pregnant women, these conditions developed.

Tenosynovitis. Many physicians are unfamiliar with de Quervain's disease—stenosing tenosynovitis or tendovaginitis of the tendons of the extensor pollicis brevis and the abductor pollicis longus. These tendons pass in a common sheath through a groove on the most lateral portion of the radial styloid process. Similar lesions may occur in the tendons of the flexor pollicis longus, extensor carpi ulnaris and flexor carpi radialis. [Would it not be better to discard the term "de Quervain's disease," and describe these conditions as stenosing tenosynovitis of the particular tendon affected?—Ed.] Reported were five cases by Diack and Trommald and one by McDonald and Stuart. About 70 per cent of such patients respond to conservative therapy, "immobilization of wrist and abducted thumb in plaster for six weeks." Simple incision of the sheath is almost always satisfactory.

Osteochondritis. The association of chondritis with internal derangement of the knee was discussed.[216] Osteochrondritis of ankle (two cases),[124] knee (one case) [124] and elbow joint (one case) [552] was described. Freund discussed the relationship between osteochondritis dissecans of the head of the femur and partial idiopathic aseptic necrosis of the femoral head. Four cases of osteochondrosis deformans of the tibia were described.[44]

Charcot's (Tabetic) Arthropathy. This was discussed under Syphilis of joints.

Pulmonary Osteo-Arthropathy. A case of pulmonary osteo-arthropathy secondary to carcinoma of the thymus was noted (Miller). In another case no primary disease was demonstrated although the patient had hypercalcemia.[391]

Sclerodactylia and Scleroderma. The theory that dermatomyositis and symmetrical scleroderma with sclerodactylia are identical was advanced by Dowling and Griffiths who reported the pathologic findings from biopsy in

two cases, and stated their belief that the muscle changes are degenerative, not inflammatory. Ochsner and De Bakey considered scleroderma related to hyperparathyroidism.

Protrusio Acetabuli (*"Otto Pelvis"*). An exhaustive, profusely illustrated discussion of acetabular deformities was presented by Gilmour who distinguished primary from secondary protrusions. The former are related to development of the bony pelvis, are commonly bilateral and preponderate in females. The latter are due to destructive disease of the hip or to trauma, and are usually unilateral. Twelve case reports were presented and the clinical features of 41 cases were reviewed.

Cutis Elastica (*Dermatorrhexis, Ehlers-Danlos Syndrome*). Cases were reported by Smith [703] and Burrows and Turnbull but nothing new was added to that noted in previous Reviews.

Congenital Anomalies: 1. Amyoplasia Congenita. Multiple congenital articular rigidity (myodystrophia foetales deformans, arthrogryposis multiplex congenita) is a symptom complex which includes congenital, symmetrical, joint rigidities of various degrees without inflammatory changes. It is believed to be an aplasia. A case was described.[17]

2. Discoid Cartilage (*Trigger Knee*). This condition represents a persistence of the embryonic external semilunar cartilage. Three cases in which surgical treatment was used were described.[567] The comparative anatomy of the knee joint in relation to congenital anomalies was discussed.[670]

Ochronosis. A typical case of alkaptonuria with ochronosis was described by Bhatia. The patient had been bedridden for 10 years because of vague pains all over the body and arthritis of the knees and interphalangeal joints. Present were purpuric rashes for which there was no explanation other than the ochronosis.

Diseases of Bursae

General Comment. A good synopsis of the anatomic and etiologic types of bursitis was given by Ghormley who discussed treatment of the various types including "housemaid's knee" (prepatellar bursitis), "miner's elbow" (olecranon bursitis), and "Albert's disease" (retrocalcanear or deep Achilles bursitis). Infection, trauma and metabolic disturbances (e.g., gout) are chief causes. The pathologic reaction varies with the cause and stage of the process. An important complication is intrabursal calcification which develops "when sufficient fibrosis exists, when the hydrogen ion concentration is ideal and when the blood supply is inadequate." [76, 807] Treatment depends on the nature and severity of the bursitis, and varies from surgical procedures such as incision, excision or needling to conservative measures such as rest, heat, roentgen therapy.[307, 505]

Current writers [76, 114, 141, 548] considered trauma a more important cause of bursitis than infection. A common sequence of events is trauma to the bursa or to tendons adjacent to the bursa, partial rupture of a tendon already

somewhat degenerated by age, the development of inflammation, adhesions and calcium infiltration of the *tendon* with *secondary* irritation or inflammation of the bursa, and spasm and contractures of adjacent muscles. For this reason it is not entirely correct to speak of, e.g., " subacromial bursitis " because other structures besides the bursa are primarily or secondarily affected.

Special Types of Bursitis. " Tennis elbow " was discussed briefly.[193, 307, 315] Conservative measures (rest, perhaps splinting, heat, massage) are preferred to surgical excision.

Inflammation in the bicipitoradial and interosseous bursae of the elbow may cause nontraumatic paralysis of the dorsal interosseous nerve with progressive paralysis and atrophy of phalangeal extensors, according to Weinberger.

Cases of metacarpophalangeal or interphalangeal bursitis were reported.[188, 381, 406] An operation for Achilles bursitis was described.[831]

Diseases about the Shoulder Joint: The Painful Shoulder

" Subdeltoid or Subacromial Bursitis." This is more than a bursitis; indeed in some cases bursal involvement is either absent or of minor importance. Writers again stressed the fact that the primary lesion is generally a partial or complete rupture of the supraspinatus tendon near its insertion, with subsequent inflammation therein and in adjacent tissues, leading to adhesions and disability of the abductor and rotator muscles of the shoulder girdle.[8, 76, 141, 399, 548] The various symptoms produced by these lesions and the differentiation between partial and complete ruptures were described in detail (as in previous Reviews).[8, 114, 141, 313, 548, 634, 716, 830] In some cases symptoms resemble those of " brachial neuritis " or the " scalenus anticus syndrome " (pains in neck muscles, scapular region and sometimes down the arm to finger tips).[76]

Treatment. For acute cases rest, heat and narcotics were generally advised, but the shoulder should be rested in abduction, not adduction.[193, 195, 197, 203, 634] Short wave therapy,[113] conventional diathermy,[769] fever therapy [102] and roentgen therapy [381] were recommended. Instead of rest, Moseley advocated daily motion, from the onset of treatment, made possible by using injections of novocaine and diathermy. In acute cases (with or without calcium deposits) unrelieved by these measures, several physicians strongly recommended needling and lavage with saline and novocaine.[76, 141, 634, 729, 830] Relief is often prompt and complete. Others [114, 313, 716] favored early surgical repair in cases of partial, as well as of complete, rupture of the supraspinatus.[399] Horwitz [399] recommended operation only for patients under 40 years of age.

For more chronic cases intensive physical therapy, curettage of calcium deposits [634] or manipulation with [141, 525, 634, 784] or without [8] anesthesia was advised. Roentgen therapy was favored by others [75, 188, 505, 830] as a " com-

paratively specific" means for relieving pain and fostering absorption of calcium deposits. On the theory that "allergy of the climacterium" caused painful stiff shoulders, Voight used large doses of progynon and local histidine iontophoresis; restitution of normal motion was claimed [no statistics given—Ed.].

Pain about shoulders may be caused by lesions other than in the supraspinatus tendon, among them fibrositis of adjacent muscles, cervical hypertrophic arthritis, and contracted, hypertrophied or anomalous scalenus anticus muscle.[8, 313, 407, 472, 716]

Peritendinitis Calcarea. Bursitis calcarea is probably a manifestation of this condition which affects hips and knees as well as shoulders; calcium deposits often rapidly disappear after roentgen therapy according to Copland and Michel.

[Such deposits often disappear rapidly spontaneously.—Ed.]

Diseases of Muscles and Fibrous Tissue

A clinical pathologic study of muscular diseases was made by Geschickter and Masseritz who classified their cases of myositis as follows:

	Cases
Acute:	
Nonspecific, abscess formation	6
Nonspecific, no abscess formation	2
Chronic:	
Nonspecific, abscess formation	2
Nonspecific, no abscess formation	17
Tuberculosis	15
Syphilis	8
Trichinosis	6
Torticollis	17
Volkmann's ischemia	7
Myositis ossificans	25
Diphtheria	1
Progressive muscular dystrophy	2

They emphasized the difficulties of diagnosis in the chronic group, and, in view of their frequency, urged that tuberculosis, syphilis, trichinosis and the exanthematous diseases be considered, and biopsy be done if diagnosis is obscure. Two cases of trichinosis were noted in which findings suggested the presence of arthritis without clinical symptoms of trichinosis. Diagnosis was made by biopsy. A classification of muscle tumors was also given.

Diseases of Muscles Caused by Trauma

Rupture of Muscles. Symptoms due to partial or complete rupture of various muscles were described and treatment was outlined.[313]

Myositis Ossificans. Eleven cases of this disease following injury were reported by Hirsch and Morgan. A bony mass was removed surgically in all cases. Cartilage and fibrocartilage were found in varying degrees of differentiation. Fibrocartilage is a normal constituent of the insertions of many tendons in which traumatic ossification occurs. Reactive or repara-

tive growth of these tissues initiated by trauma provides a simple explanation for the traumatic ossification. Complete immobilization of the involved region was Kleinberg's[458] early treatment of choice.

Ossification of the anterior cruciate ligament following injury was described.[300]

Fibrositis

Fibrositis accounts for from 30 to 60 per cent of all cases of rheumatic diseases according to some physicians.[7] [Two of us, W. B., and M. H. D., do not agree; we believe that the term "fibrositis" is too loosely used and that many cases of "fibrositis" represent other conditions.—Ed.] About 75 per cent of the cases encountered at the arthritis clinic, De Paul Hospital, St. Louis in 1938 were of fibrositis. It is surprising therefore that of all the articles under review only three were concerned chiefly or solely with fibrositis.[7, 210, 555] Fibrositis was classified by Abel, Siebert and Earp thus: (1) primary fibrositis; an affection of fibrous tissue independent of atrophic arthritis or any other articular disease; in these cases atrophic arthritis practically never develops later; (2) secondary fibrositis; fibrous tissue changes secondary to atrophic arthritis, specific infections, trauma, etc.; (3) senile fibrositis; fibrositic changes which occur with age. Of their 71 cases these writers called 55 primary and 16 secondary (20 acute and 51 chronic).

[It is not clear whether they listed their cases of senile fibrositis as primary or secondary.—Ed.]

Symptoms. These were described[7, 555]; morning stiffness of muscles and joints, "jelling" after rest, general exhaustion which is usually worse as the day wears on, moderate relief from moderate exercise, exacerbations from overexertion. Symptoms of fibrositis of muscles of the neck and fibrous tissues of the scalp which produce "rheumatic headaches" (first described in 1615) were discussed by Cyriax.

Pathology. In an unstated number of cases Abel, Siebert and Earp made muscular biopsies. In the acute and subacute cases hemorrhages, hyperemia, serofibrinous exudate between the muscle bundles, newly formed fibroblasts, mild degenerative changes in the muscle, swelling and loss of cross striation and a few inflammatory cells, chiefly lymphocytes were found. In the chronic cases fibrosis of muscle fascia and intramuscular septa with separation of muscle bundles, marked degenerative changes in muscles including complete loss of cross striation, hyalinization, and fat between muscle bundles were present. [Then why isn't this "myositis," not "fibrositis"?—Ed.] At necropsy of patients with osteo-arthritis who had complained of backache, sections of muscles showed definite fibrositis. For others with equal or greater changes from osteo-arthritis who had not complained of backache there was no associated fibrositis of the muscles.

[Unfortunately the authors summarized these findings too briefly for them to be of much value. No case reports were given with related data on pathology. The pathologic findings were classified as acute or chronic, but it was not stated when

they were from cases of primary or secondary fibrositis. It is difficult to believe that the muscular lesions of primary fibrositis (no muscle atrophy or notable flexions) are identical with those of fibrositis secondary to atrophic arthritis.—Ed.]

Etiology. The relation of fibrositis to infected foci was considered doubtful by Abel, Siebert and Earp: "The pathologic findings in our cases correspond more with an allergic response than an infection." [But the pathologic reactions described above do not conform to those of orthodox allergy.—Ed.] According to Levinthal "fibrositis" (type not stated) may represent an anaphylactic reaction to several unknown antigens but seems to be related to streptococcal infections in 25 per cent of cases [no proof—Ed.]. Chilling, respiratory infections and influenza are common precipitating factors. According to Pennington fibrositis is only the pathologic expression of a normal physiologic fatigue process related to an inefficient mechanism in both skin and lymphatic drainage of, possibly, lactic acid; the development of better chemical methods for analyzing sweat may permit one to prove this idea. Rosenow noted 64 cases of fibromyositis associated with encephalomeningoradiculitis, the result of epidemics of poliomyelitis, 1934 to 1936. Symptoms were multiple and included pains in back, extremities, heels, and wrists and in several cases fibrous ankylosis of interphalangeal joints preventing fist-clenching. Extensive bacteriologic studies were made on a streptococcus isolated from foci. Shorbe noted nine mildly febrile cases of lumbar myofasciitis possibly due to brucellosis.

Treatment. Conventional treatment was outlined[7, 33, 555]: removal of infected foci, use of physical therapy, especially massage, use of warm clothing; avoidance of chilling, drafts, colds and influenza. No special diet was generally advocated, but Bach[33] prescribed a lactovegetarian diet in cases presumably caused by intestinal putrefaction. [He did not say how this could be proved or satisfactorily presumed.—Ed.] Neligan and Cyriax upheld the English view on the great value of heavy massage: in cases of "rheumatic headaches, provided the correct spots are massaged firmly and persistently, there should be next to no failures." According to Crichton-Miller patients whose fibrositis fails to respond to physical therapy may have some psychologic reason for wishing to remain ill or to continue treatments; some of the motives were discussed. Others[7] considered heavy massage provocative of exacerbations, and used light massage only, and that only in chronic cases. In acute cases moist heat is preferable to diathermy.[195, 197] Recommended were autohemotherapy and/or fever therapy,[421] bee venom,[12] streptococcal vaccine,[803] Crowe's vaccine[7] and colloidal sulfur.[282] For lumbar fasciitis Creer and Romer recommended early manipulation under anesthesia as productive of much quicker results than those from rest, heat, etc.: it may give "instantaneous relief." [The technic was not given nor the reason why such therapy should give results.—Ed.] Injections of procaine were strongly recommended by Steinbrocker for lumbar fasciitis, by Cyriax for cervical fibrositis. For diffuse lumbar or gluteal fibrositis Steinbrocker made deep injections of 10 c.c. of 2 per cent procaine with 25 to 100 c.c. normal saline

solution. Painful tender nodules were penetrated with a needle; 5 to 10 drops were deposited therein and 3 to 5 c.c. injected around the nodule. For nodules unaffected thereby he injected 3 to 6 mm. of 95 per cent alcohol into the nodule, 5 c.c. aqueous procaine solution around the nodule. Of 15 patients with fibrositis so treated 10 obtained "marked or complete relief." Cyriax infiltrated persistently tender cervical spots in muscles with 1 in 200 watery solution of procaine or 1 in 50 solution of procaine in olive oil.

Miscellaneous Diseases of Muscles

Dermatomyositis. Two cases of dermatomyositis with progressive scleroderma were reported by Dowling and Griffiths who consider dermatomyositis and progressive symmetrical scleroderma the same disease. Sheldon, Young and Dyke reported the clinical and pathologic findings in a case of acute dermatomyositis with a skin rash, attacks of edema in the leg muscles, and severe muscular weakness with fibrosis: at necropsy generalized reticulo-endotheliosis with localization in liver, spleen and mediastinum was found. It was suggested that dermatomyositis may represent a derangement of the reticulo-endothelial system. Because of profound weakness, malaise, gastrointestinal disturbance, loss of weight, pigmentation of skin and postural hypotension, a case of dermatomyositis and scleroderma, proved at necropsy, was first diagnosed as Addison's disease.[751] [Cases of pigmented scleroderma suggesting Addison's disease are not uncommon.—Ed.] Three cases of dermatomyositis among children were reported by Bruce; all had identical retinal lesions with extensive regions of whitish exudate and small hemorrhages. Other cases of dermatomyositis were reported.[60, 142, 379, 445] A case of poikilodermatomyositis was reported by Guy, Grauer and Jacob in which there were all the features of dermatomyositis plus poikiloderma; they implied that the latter is a variant of the former.

Miscellaneous Conditions. Eighteen cases of *tropical pyomyositis* unrelieved by malaria and antisyphilitic treatment, responded dramatically to sulfapyridine.[242] Five cases of *epidemic myalgia* (devil's grip, pleurodynia) occurring in the same family were reported.[404] Two cases of *myositis fibrosa* were reported.[80, 712]

Miscellaneous Conditions

Periarteritis Nodosa. "Arthritis" and muscle pains, "polymyositis," may occur in this disease; hence rheumatologists should become familiar with it. Among the 11 cases reported this year diagnosis was unsuspected until postmortem examination in seven, was made by biopsy in two, and suspected antemortem in two others. Only eight cases of periarteritis nodosa have been recognized among 53,000 patients at Peter Bent Brigham Hospital.

Harris, Lynch and O'Hare reported six cases. The complete confusion in symptoms is best illustrated by briefing their six cases: Case 1: Chinese woman with sea-

sonal allergic rhinitis, chronic glomerulonephritis and cirrhosis of liver; death from uremia: widespread periarteritis nodosa at necropsy. Case 2: young Greek student with polyarthritis, low grade fever, leukocytosis, splenomegaly and cutaneous nodules; periarteritis nodosa at biopsy; patient recovered and has been well four years. Case 3: a surgeon complaining of exhaustion, arthritis, fever, tachycardia, hypertension and anginal attacks; signs of glomerulonephritis; periarteritis nodosa clinically and at necropsy. Case 4: woman with hypertrophic arthritis, emphysema and chronic myocarditis; death from congestive heart failure and bronchopneumonia; periarteritis nodosa at necropsy. Case 5: man with fever, foot and wrist drop, and chronic glomerulonephritis; death from bronchopneumonia; clinical diagnosis, polyneuritis; periarteritis nodosa at necropsy. Case 6: fireman with gastric ulcer and hematuria; death from uremia; periarteritis nodosa and gastric carcinoma at necropsy.

Harris, Lynch and O'Hare, having studied all cases reported before 1938, concluded that there is no characteristic symptomatology. Of the 101 reported cases recovery occurred in 10. Males predominated 3 to 1. Ages were from 6 to 71 years; average was 36.9. *"Arthritis" occurred in 27 per cent.* [Its characteristics were not described.—Ed.] Common symptoms, in order of frequency, were fever, leukocytosis, albuminuria, abdominal pain, edema, loss of weight and hypertension. Most frequent organs involved were kidneys in 87 per cent, heart in 84 per cent, liver in 71 per cent, spleen in 31 per cent, lungs in 25 per cent.

One fatal case of periarteritis nodosa with livedo reticularis, was seen (Ketron and Bernstein). Other cases were reported [143, 279, 610, 653, 805]: in one the first diagnosis was "arthritis." [547] "The history of periarteritis nodosa disposes to clinical humility. All that can be said is that it is a freakish vascular disease of unknown origin likely to prove fatal in a few weeks or months, occasionally years, and producing extremely varied clinical manifestations with no known preventive nor any known cure" (Fitz, Parks and Branch).

Aseptic Bone Necrosis. Four cases of long standing caisson disease producing aseptic bone necrosis and "arthritis deformans" (i.e., hypertrophic arthritis) were reported by Kahlstrom, Burton and Phemister.

Bone necrosis was produced by injury of tissues from the release of nitrogen bubbles due to too rapid decompression. Uncertainty prevails as to whether the bone damage is due to the obstruction of end-arteries by gas embolism or by direct pressure on blood vessels and other tissues after liberation from solution in the marrow fat. One case came to necropsy; in another biopsy was done on the involved femur. When necrotic bone was situated in the epiphyses and bordered on joints, varying amounts of collapse occurred. Articular cartilage overlying the involved parts had broken down and had been replaced by fibrocartilage; a more or less extensive arthritis deformans resulted. This supported the theory that arthritis deformans may be due to vascular blockage and necrosis of bone underlying articular cartilage. Attempts to produce bone lesions in dogs by air emboli were unsuccessful. In three cases with no history of caisson disease, Kahlstrom, Burton and Phemister noted almost identical findings as those found in caisson disease. [They were the first such cases reported.—Ed.] Roentgenograms revealed lesions similar to those just described for caisson disease, areas of massive infarction of bones with the development of arthritis.

Disseminated Lupus Erythematosus. This may produce symptoms resembling rheumatic fever, atrophic arthritis, or fibrositis.

A case with postmortem findings was reported by Contratto and Levine. Because of a prolonged P–R interval (0.24 sec.) and fever associated with joint pain and swelling, the initial diagnosis was rheumatic fever [a not unusual error.—Ed.]. The true diagnosis later became evident with the appearance of the cutaneous lesions. Roentgen therapy was given over the ovaries in an attempt to sterilize the patient. This was done because the authors had never seen this disease except in women between the onset of puberty and the beginning of the menopause. Temperature dropped rapidly after roentgen therapy; the patient felt much improved for two days, but lobar pneumonia developed and the patient died. Necropsy disclosed lupus erythematosus disseminatus but no evidence of rheumatic fever. The only pathologic feature now recognized as specific for this disease is the skin lesion.[544] A classification with illustrative cases was given by Urbach and Thomas. Sulfanilamide seemed useful to some,[715] but not to others.[816]

Variable Symptom Complex. A variable symptom complex of undetermined etiology with fatal termination was described by the Reifensteins who added a case to 17 in the literature. Articular manifestations (usually polyarthritis) and pleuritis were present in each case. Synovial hypertrophy, subperiosteal bone formation and capsular edema have been noted. In most cases prolonged fever, polyserositis, erythematous cutaneous lesions, nephritis, anemia and a remittent cachectic course with fatal termination occurred. This variable group of symptoms has been called many different names (Libman-Sacks' disease, Pick's disease, lupus erythematosus, periarteritis nodosa, etc.). The cause is unknown. Such cases should be grouped for further study.

[Christian's case, 1935, was noted in our Third Review. The case of the Reifensteins may well have been one of lupus erythematosus.—Ed.]

Multiple Myeloma. This may produce symptoms suggestive of atrophic arthritis as it did in the cases of Tarr and Ferris: nodular deposits of amyloid were in and about joints.

Other Studies on Joints and Related Tissues

Articular Roentgenography. An improved technic for roentgenograms of knee joints was again [5] described.[392] By using a better articular position clearer visualization of joint space, joint mice, loose bodies, etc., is obtained. "Pneumarthrography" was considered valuable in the diagnosis of athletic and industrial injuries.[361] Lindblom used a contrast medium soluble in water (perabrodil) for injection into knee joints without serious reactions. Crucial and tibial collateral ligaments were thus visualized.

Articular Physiology. After studying synovial sarcomas Berger [67] posed these questions: 1. Is the synovial membrane a simple endothelium, a modified cartilage, a reticulohistiocytic or a truly autonomous and specific tissue? 2. Is the synovial fluid the result of a direct or indirect secretion and what is the mechanism of mucin formation?

He concluded that synovial tissue has peculiar characters setting it apart as a variety sui generis of the reticulo-endothelial system. He proposed the designation "synoviothelial" for synovial tissue, as employed by Hueck and in accord with Vaubel's conception of synovioblasts. He concluded that mucinogenesis is entirely different from mucous secretion in glandular cells and may be comparable to the intercellular substances appearing in mesenchymatous tissues. Synovial fluid may be analogous to cartilaginous and osseous intercellular substances except that in synovial tissue the substance remains liquid.

The absorption of mecholyl from knee joints of cats was reported.[626] Experiments were carried out on normal joints, joints mildly inflamed by saline injections, and joints experimentally inflamed by aleuronat. From all normal joints mecholyl was absorbed readily, more rapidly with exercise. Inflammation increased the rate of absorption both at rest and after exercise. Other experiments with adrenalin, pituitrin and pilocarpine led to the conclusion that absorption was largely by the blood stream, a very small amount being absorbed slowly through lymphatics. Bennett and Shaffer studied the transference of proteins from blood into knee joints of rabbits, also the passage of protein into aqueous humor, spinal fluid and urine. Crystalline egg albumin was transferred from the vascular system into the knee joint within five minutes. Amounts of egg albumin in joints tended to vary directly with that in serum. Egg albumin was also speedily removed from the joint and was excreted largely unchanged in urine. Similar results with isotonic solutions were reported.[277] Meyer, Smyth and Dawson isolated from synovial fluid a mucopolysaccharide apparently similar to that in vitreous humor, umbilical cord, and also in group A hemolytic streptococci. Theories on the nature and origin of synovial fluid were reviewed by Ropes, Bennett and Bauer who analyzed synovial fluid from the astragalotibial joint of cows. They concluded that normal bovine synovial fluid is a dialysate of blood plasma. Unlike other dialysates synovial fluids contain mucin of unknown origin. Mucin plays a definite rôle in the exchange between blood capillaries and the joint space.

Burman and Kling studied the excretion of Evans' blue dye into synovial effusions of five patients with atrophic arthritis; amounts of the dye in effusions were directly proportional to the activity of the rheumatic process. Postmortem study of a case of spastic quadriplegia and athetosis permitted Freund to study joints, some long disused, others long overused. The study indicated that joint cartilage degenerates and is replaced by fibrous tissue if it lacks contact with its antagonist. The same changes occur if pressure is too great or if near normal pressure be maintained for too long a period continuously. "There is nothing specific to hypertrophic arthritis. Any marked alteration of function for a long period (infra- or ultra-physiologic demands) leads to degenerative changes of joint cartilage and may be followed by the whole syndrome of fully developed arthritis deformans."

The lateral parts of joint cartilage, according to Fisher,[277] receive nourishment from the circulus articuli vasculosus; the central portion is less well

nourished by synovial fluid; hence there are differences in rate of repair of the central and lateral parts. An experimental injury to the central portion remains unhealed for a long time, then healing occurs largely by connective tissue formation. The same injury to the lateral portions heals more rapidly with true proliferation of cartilage. Removal of the central portion is followed by a compensatory proliferation of the lateral margins, thus forming a typical osteo-arthritis.

[One of us, J. A. K., believes that this marginal proliferation is not compensatory but due to the increased blood supply incident to repair of the defect.—Ed.]

Abercrombie discussed the influence of morphologic structure on the pathology of joints, the relation of the former to the frequency and location of fibrositis and arthritis in certain sites.

Articular Function. A new instrument for measuring joint motion was described.[813] Degrees of normal motion of all joints as measured by this method were tabulated. Montgomery discussed the knee from a historical and philosophic viewpoint.

Experimental Arthritis. 1. Infectious. A spontaneous polyarthritis in rats was studied by Findlay and associates who isolated from joints a pleuropneumonia-like organism which reproduced the disease when injected into pads of mice and rats. Other species of animals were unaffected. The experimental arthritis was dramatically affected by gold salts but not by sulfonamide compounds. Sabin produced a proliferative chronic polyarthritis resembling somewhat human atrophic arthritis by injecting mice with a filtrable pleuropneumonia-like organism isolated from the brain of a normal mouse. The experimental arthritis was produced almost constantly in 150 mice by one intravenous or intraperitoneal injection. It was migratory, chronic and progressive, often with fusiform swelling and ankylosis. No tissues but joints seemed affected; all the 150 mice appeared in good health; none died. A second strain of the organism produced a disease much more like rheumatic fever. [Sabin could not isolate such organisms from patients with rheumatic fever or with atrophic arthritis, but urged the application of such studies to human arthritis.—Ed.] Collier also observed a similar spontaneous polyarthritis in rats which he reproduced by injection of sterile joint material into pads of other rats; no organisms were isolated. Others [627] reported similar findings.

[These studies of Collier, Sabin, Findlay and their colleagues have aroused much interest. Although Sabin was unable to do so, Swift and Brown reported the apparent recovery of pleuropneumonia-like organisms from cases of rheumatic fever, and erythema nodosum. But they subsequently found that the organisms in reality came from mice, not from the rheumatic patients. Despite this these studies are important because the polyarthritis in mice and rats strongly resembles human atrophic arthritis, and can be reproduced experimentally. Hence an important new type of arthritis is at hand for studies on experimental therapy. In this connection the studies of Dienes and Sullivan [228, 738] are of interest.—Ed.]

Various types of streptococcal arthritis were produced experimentally. Rosenow again described his well known type of streptococcal (viridans)

arthritis. Iritis is a not uncommon complication of atrophic arthritis; hence Berens, Angevine, Guy and Rothbard carefully studied the eyes of rabbits in which experimental arthritis was induced. Ocular and articular inflammations were produced by various bacteria, especially by streptococci given intravenously. Organisms from patients with ocular disease produced more eye lesions in rabbits than strains from other sources. Animals with arthritis had no more eye lesions than animals with no arthritis; that is, no relationship was noted between involvement of eyes and joints. Infected foci were experimentally produced; few eye lesions resulted. Cecil, Angevine and Rothbard produced arthritis in rabbits by injecting into various sites, several strains of streptococci, usually hemolytic; arthritis was also produced by staphylococci and pneumococci. The disease was never migratory; joints were not affected symmetrically and those affected were not ones commonly involved in atrophic arthritis. Although the pathology of this experimental chronic arthritis was very similar to that found in atrophic arthritis, the authors did not conclude that they had produced the human type of disease; rather they concluded that the histopathology of atrophic arthritis is not specific. Gordon produced fibrositis and arthritis in rabbits by injecting a virus (*variola lapine*). Hemolytic streptococci injected with the virus produced a more marked arthritis than comparable doses of either alone. Observations on experimental type III pneumococcic arthritis were reported by Shaffer and Bennett.

2. Chemical and Nutritional. The Silberbergs studied further [6] the effect of estrogen and anterior pituitary extract on development of bone and cartilage. In immature guinea-pigs gonadectomy caused an increased proliferation of euhyaline cartilage; hyperplasia was more pronounced in males and hypertrophy in females. Degenerative changes were more marked in males. In old animals given anterior pituitary hormone severe arthropathic changes comparable to those of human "arthritis deformans" were produced. Estrogen administered to immature guinea-pigs caused retrogressive changes, increased hyalinization and ossification indicating a premature aging of the cartilage. Previous experiments [6] on the effects of potassium iodide on cartilage were repeated on animals after thyroidectomy. Proliferation of euhyaline cartilage still occurred as it did when operation was not performed. However, the increase in the number of hypertrophic cartilage cells, the decrease of ossification and the resorption of bone which occurred when operation was not performed did not appear in the animals following thyroidectomy. Nunnemacher reported studies on the cartilage plates of long bones in the rat.

Paleopathology. A note on the relationship between oral sepsis and arthritis in prehistoric times appeared.[734]

Physiology of Muscles. Attempts were made by Maison to produce ischemic pain by injecting ammonium chloride, potassium chloride and sarcolactic acid into muscles: it was concluded that they are not responsible for

such pain. In a paper which cannot be reviewed adequately herein, Wright discussed the mechanism of pain, particularly that arising in muscle, the metabolism of skeletal muscle and the properties of muscle extracts, the interchange of fluid between blood and tissues, the flow of lymph, the rational basis of massage, and the effects of reactive hyperemia, heat and artificial fever.

Finding no changes of bones or joints in the hind limb of cats following complete denervation (lumbar sympathectomy and section of fourth lumbar to third sacral "dorsal roots"), Corbin and Hinsey concluded that bones and joints are not supplied with nerves having a specific trophic function.

Campaign against Rheumatism

The literature under review, written before the Blitzkrieg, showed no influence of the war on the campaign against rheumatism. [But letters received recently from British and other European sources indicate an almost total cessation of the campaign.—Ed.] Davidson repeated his plea for a British national campaign against rheumatic diseases, emphasizing the inadequacy of hospital facilities for British arthritics. This same difficulty exists in the United States, where most hospitals are financially and psychologically "geared" only for the care of acute illnesses and injuries and have little room for, and less interest in, cases of chronic arthritis. According to Fantus large city hospitals, such as the Cook County, can accept arthritics only for a short examination or brief period of treatment. Hospitals should meet their responsibilities more adequately and provide not only ample outpatient facilities for continued therapy, but also special units for research and hospital treatment. English physicians joined Davidson in his insistence that hospital and other facilities for rheumatic patients are so grossly inadequate in England that the most urgent need for effective action is in the political, rather than in the medical, field. "If all the money wasted on [advertised remedies] was applied to a fund it would be possible to establish a central clinic in each town." [59] The British advertisers' association has barred advertisements of remedies to "cure," "banish" or "conquer" chronic arthritis.[254]

"The treatment of chronic rheumatic diseases is the business of the Nation and can no longer be left entirely to voluntary effort. Like the treatment of tuberculosis it must be combated by government, county councils, boroughs and municipalities. The public must be educated to the need for 'a mass attack' on this scourge—for it is a scourge": such was Pringle's opinion. Smart sought changes in the British Insurance Act so that physicians could prescribe, with governmental aid, physical therapy, and not just pills, for arthritics. He also urged the establishment in England of more industrial clinics where patients with early traumatic or infectious rheumatism could get early and adequate treatment: much money would be saved for industry. The two Travelling Fellows of the Empire Rheumatism

Council, Tegner and Duthie, expressed complimentary opinions of American arthritis units visited by them and recommended the establishment in England of similar units.

Despite the imminence of war the Empire Rheumatism Council prosecuted its campaign with vigor, raised large sums of money for fostering rheumatism units and research, and established affiliations in various Dominions and Colonies. Their broad, excellent plan of action, heartily sponsored by the Duke of Gloucester, the Lord Mayor of London and others, was again described.[257, 397] Despite the approach of war the British effort continued unabated. As the Duke of Gloucester[257] said, "It is surely proof of the sober strength of mind of the British race that, despite circumstances of no little discouragement, we can give our attention to a campaign which aims to enlist our energies against the common enemy of human happiness —the forces of destructive disease. We have good cause to believe that the problem of rheumatic diseases will be solved by persevering effort." Unfortunately these brave words cannot now be implemented by action anywhere in Great Britain or Europe. Until peace returns the responsibility of continuing the campaign rests on the medical profession of the Americas. It is our belief that the campaign will be prosecuted here with increased vigor.

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CASE REPORTS

THE SIGNIFICANCE OF SPLITTING OF THE P-WAVE IN THE ELECTROCARDIOGRAM *

By GEORGE BACHMANN, M.D., F.A.C.P., *Atlanta, Georgia*

NOTCHING, bifurcation and splitting of the P-wave have been observed in a variety of cardiac conditions. The feature which is common to all and which is responsible for the abnormality can best be understood by considering a few facts relative to the time of onset of the contraction of the two auricles and the modifications that follow experimental interference with the spread of the wave of excitation from one auricle to the other.

An old observation of Chauveau [1] made on the horse in 1894, that the right auricle contracts before the left, was confirmed experimentally by Fredericq [2, 3] using the dog's heart, and subsequently by his pupils Schmidt-Nielsen [4] and Stassen,[5] who found a time interval of 0.03–0.04 sec. Garten [6] and Erfmann [7] obtained by local derivation of the action current, an interval of 0.013–0.014 sec. Lewis, Meakins and White [8] concluded from their measurements that the question as to whether right or left auricle first contracts is unprofitable since "certain portions of the right auricle contract before certain portions of the left auricle, and vice versa." But, as was pointed out by the writer,[9] although it is doubtless true that individual parts of the two auricles begin their contraction at various times in reference to each other, it is the resultant of these differently timed contractions that determines the contraction of the chamber as a whole. A priori reasoning would lead one to expect that the right auricle being nearer the site of impulse formation would be the first to receive the excitation and would therefore contract before the left. Using the suspension method in 12 dogs, the author was able to confirm the observation that the right auricle contracts before the left. An average of 332 measurements yielded a time interval of 0.013 sec. The author was also able to demonstrate that the most direct path of conduction from the sino-auricular node to the left auricle is the interauricular bundle—a bundle of muscle fibers that stretches from the head of the S–A node to the base of the left auricular appendage. Clamping this bundle causes a marked delay in the conduction of the impulse to the left auricle so that the interauricular time interval is prolonged from two to four times the normal average.[9] The same results were obtained when Wiggers' miniature myographs and segment capsules were used. (See figures 1 and 2.) That in spite of the crushing of this band of muscle the impulse reaches the left auricle indicates that other less direct pathways exist.†

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† The various muscle bundles connecting the two auricles have been described by Papez.[10] Besides the interauricular bundle, they include chiefly the left anterior crest and the septo-pulmonary bundles. Both sets of fibers intermingle more or less with those of the interauricular bundle.

This observation has since been confirmed by a number of investigators. In this connection the work of Rothberger and Scherf [11] is of special significance as their experiments included a study of the electrocardiogram. So far as this feature of their work is concerned, they found that ligation of the interauricular bundle was followed by splitting of the P-wave, which was often flattened out and at times became negative. Certain variations in their results led these investigators to ligate various branches of the coronary arteries that supplied the region of the heart under consideration. The effects observed were uncertain,

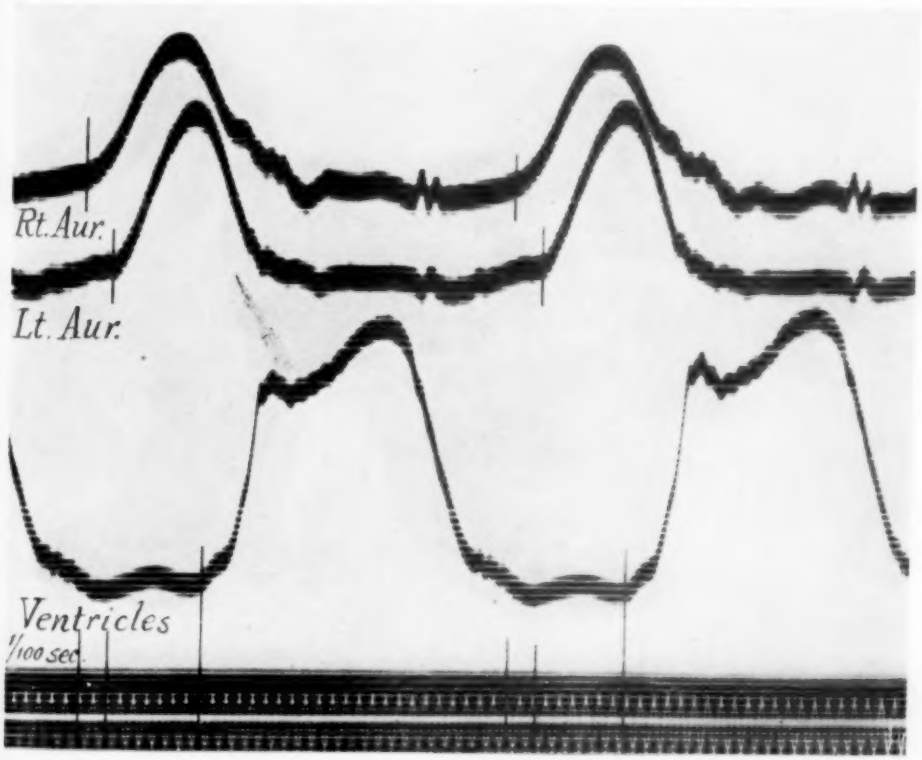

FIG. 1. Record of contraction of auricles and ventricles of the dog's heart. The left auricle contracts 0.02 sec. after the right auricle.

but clamping or ligation of the bundle in places where no blood vessels were visible led to the usual changes. This question was taken up subsequently by Condorelli [12] who described a branch of the left coronary artery under the name of ramus recurrens interauricularis, ligation of which caused the same effects as injury to the interauricular band. In the course of his experiments, there occurred on occasion a fibrillation of the left auricle while the right auricle continued beating rhythmically.

There can be little doubt, therefore, that direct injury to the interauricular bundle or serious interference with its blood supply will delay interauricular conduction and that this will manifest itself in the electrocardiogram as a splitting of the P-wave. The slight notching near the summit of P seen at times in the

normal electrocardiogram is probably due to an incomplete fusion of the potentials developed in the two auricles. Whether in such cases the interauricular time interval is greater than the average remains to be investigated.

A number of clinicians have in recent years directed their attention to the mechanism of bifurcation or complete splitting of the P-wave as seen in the human electrocardiogram. Among them may be mentioned Groedel,[13] who reported three cases which, after consideration of various other possibilities, he believed might best be explained as due to an exaggerated asynchronism of the two auricles owing to interference with the conduction of the excitatory process. He seemed to be unaware, however, of the pathway that might be affected. Ac-

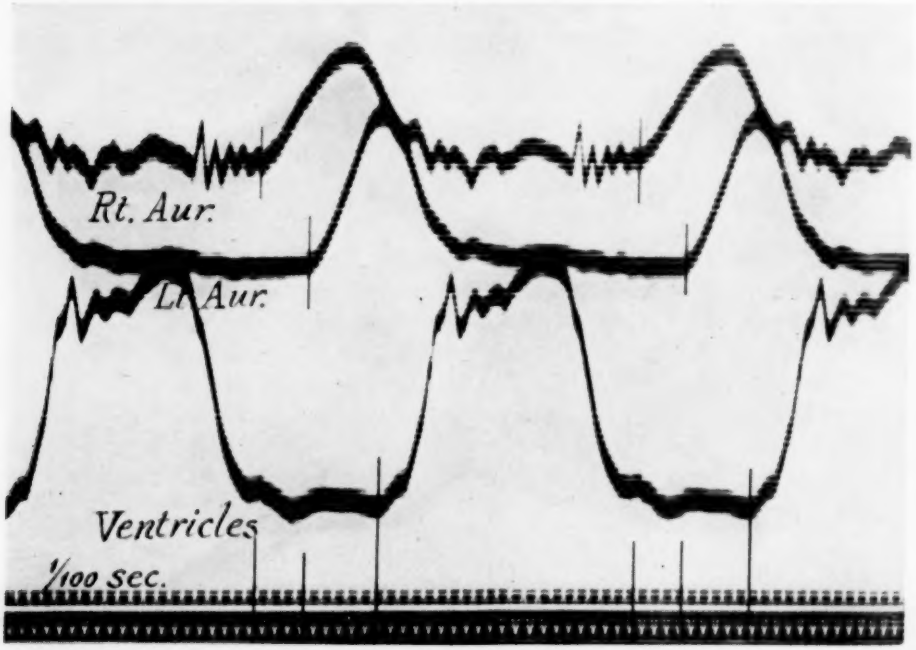

FIG. 2. Record of contraction of auricles and ventricles of the same heart as in figure 1 after clamping the interauricular bundle. The left auricle now contracts 0.04 sec. after the right auricle.

cording to Trendelenburg,[14] it is possible by cross derivation to obtain evidence of the separate and asynchronous activation of the two auricles in the normal heart. By the use of chest leads suitably placed, von Boros,[15] Laufer,[16] Laufer and Rubino [17] were able to demonstrate a prolongation of the interauricular time interval in cases in which a splitting of the P-wave occurred.

While these observations are in conformity with the experimental results presented above and point to the probability that the interference of conduction lies along the path of the interauricular bundle no one has, so far as the author is aware, studied this part of the heart in a case in which a notching or splitting of the P-wave had been observed. For this reason, the following report of histological findings in such a case is presented in the hope that further studies may be stimulated:

Case Report

The patient was a white male, 53 years old, in whom a diagnosis of hypertension had been made two years previous to admission. About a year after this diagnosis was made, he had for the first time an attack of angina pectoris. Attacks recurred at intervals of a few months. Toward the end of the year he developed signs of congestive heart failure and at the time of admission was suffering from orthopnea. A diagnosis of arteriosclerotic heart disease and congestive heart failure was made.

An electrocardiogram taken on the day following admission was interpreted as indicative of coronary sclerosis and myocardial fibrosis. There occurred occasional nodal premature beats. Aside from the changes in the ventricular complexes, including a deep Q_3, the P-wave was deeply notched, especially in Leads I and II (figure 3).

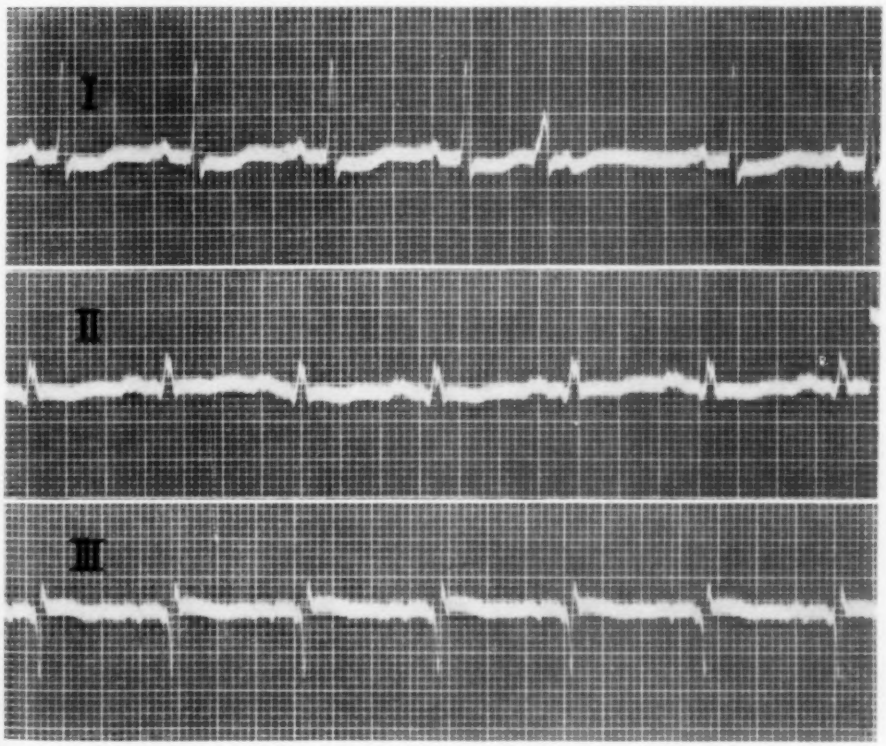

Fig. 3. Electrocardiogram obtained from the patient showing bifurcation of the P-wave in Leads I and II.

Autopsy: The patient died eight days after admission. At autopsy there were found a marked coronary sclerosis and massive cardiac hypertrophy, the heart weighing 870 grams. There were also found a well developed aortic atherosclerosis and an early arteriosclerotic nephritis. On inspection of the interauricular bundle, it was observed that a mass of fat overlaid it at about the position of the interauricular septum. The interauricular bundle had, of course, participated in the general hypertrophy.

After fixation of the whole heart in 10 per cent formalin, a block of tissue including the whole of the interauricular bundle was removed and prepared for histological study. A similar block of tissue was taken from a normal heart for com-

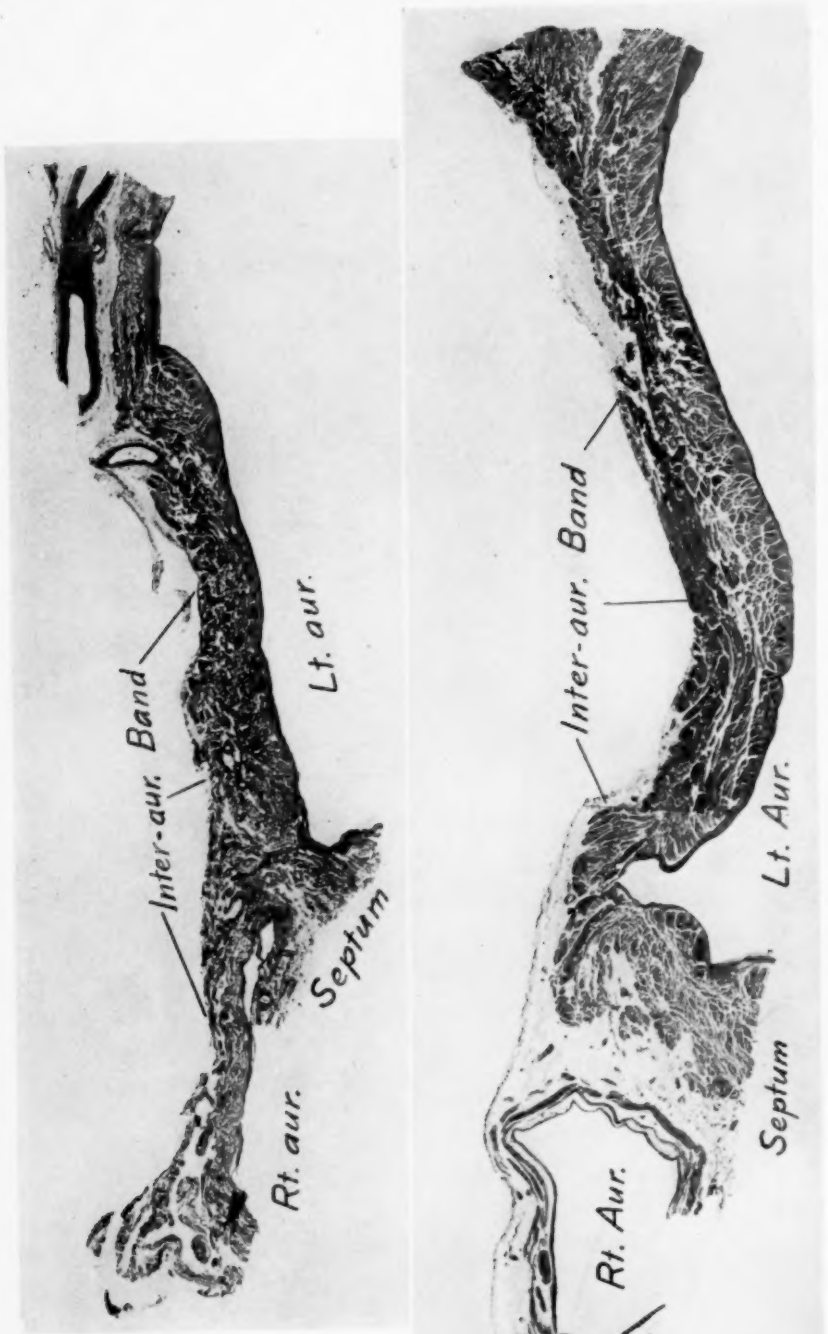

FIG. 4. Sections of the entire interauricular bundle at low magnification. Upper section from a normal heart. Lower section from the patient's heart.

parison. As these blocks were too long for section mounting, they were divided in two, immediately to the left of the interauricular septum before infiltration with paraffin. The sections were cut longitudinally 10 micra thick; every tenth section was mounted and stained with hematoxylin and eosin.

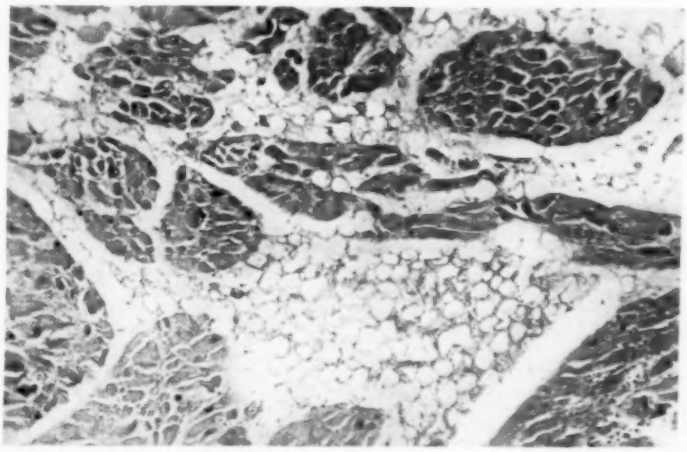

FIG. 5. Section of the interauricular bundle at the level of the septum showing fatty infiltration and separation of muscle masses. Magnification × 50.

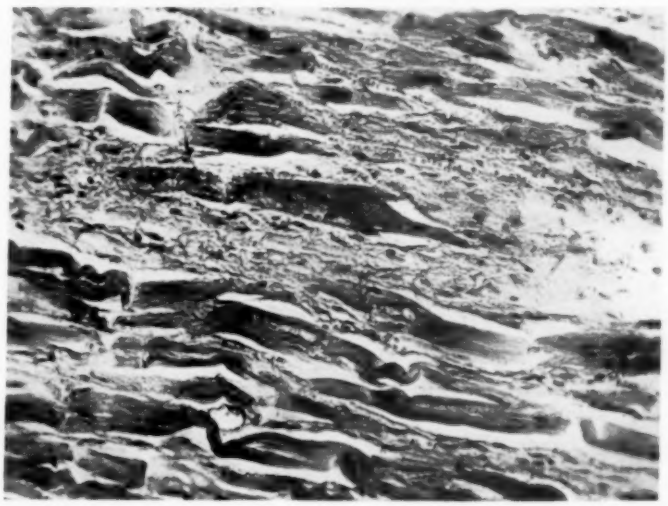

FIG. 6. Section of the interauricular bundle to the left of the septum showing swelling, fragmentation and degeneration of muscle fibers. Note the degenerated muscle fiber surrounded by connective tissue. Magnification × 150.

Histopathology: Figure 4 shows the appearance at low magnification of a section of the entire bundle in the normal and diseased heart taken at about the middle third of its thickness. Since the magnification was the same, the relative size of the two specimens is apparent. The increase in interstitial connective tissue in the pathological specimen and the scarcity of muscle tissue across the septum are all evident.

Even at this low magnification an area of the muscle below and to the right of the central line leading from the lettering "Inter-aur. Band" can be seen to differ in appearance from the rest.

Photomicrographs were made of the upper part of the septum and of the area of muscle just mentioned. The first of these (figure 5) shows how fat tissue has infiltrated into the septum and has separated the muscle fibers on their way from the head of the S–A node to the left auricle. The second photomicrograph (figure 6) shows swelling, fragmentation and degeneration of the muscle fibers. The center of the section shows a degenerated muscle cell fading into fibrous tissue. These changes were found in various degree throughout the band.

Discussion

It is evident that sufficient pathological alterations had taken place to interfere with the free conduction of the excitatory wave from the right to the left auricle and that, in accordance with the results of experiment, these alterations can account for the splitting of the P-wave observed in the electrocardiogram. This change in the form of the P-wave may therefore be expected in any condition in which interference with conduction through the interauricular bundle is likely to occur.

Aside from cardiac myopathies and disturbances of blood supply a splitting of the P-wave is often seen in mitral stenosis. It has been the custom to assign this change of form to hypertrophy of the left auricle and consequent prolongation in the spread of excitation through this chamber. The accuracy of this interpretation is doubtful. It is well known that in mitral stenosis the left auricle may become greatly distended. Rothberger [18] has called attention to the circumstance that, as a consequence of the distention, a pressure atrophy of the musculature may occur. A wide separation of muscle fibers and connective tissue replacement follow which, because of its position, must implicate the interauricular bundle. Aneurysm of the left auricle will produce the same results. In a case of this condition reported by Mahaim,[19] two P-waves separated by an interval of 0.1 sec. were recorded. Where the interauricular time interval is so greatly prolonged or where manifold splitting is seen, as in a case of mitral stenosis reported by Rothberger,[18] the damage to the interauricular musculature may include other bundles in addition to the interauricular band. In any event, the interauricular bundle is the most important part of the interauricular musculature for conduction, as it not only conducts the excitatory process at a higher rate,[8] but is also the most direct path from the S–A node to the left auricle.

Summary

Notching, bifurcation and splitting of the P-wave of the electrocardiogram are due to prolongation of interauricular conduction time, the result of damage to the interauricular bundle. A case is reported in which the electrocardiogram showed deep notching of the P-wave and in which there were found post mortem marked pathological alterations of the interauricular bundle. Experiment had shown previously that this bundle is the chief pathway for the conduction of the excitatory process from the S–A node to the left auricle.

The author is indebted to Dr. Roy R. Kracke for the courtesy of his laboratory and to Mr. T. H. Stubbs and Mr. Charles R. Ensor for their help in preparing the material for microscopic study.

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LYMPHANGITIC CARCINOMATOSIS OF THE LUNGS; CASE REPORT WITH AUTOPSY FINDINGS*

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INFILTRATION of the pleural, peribronchial, and perivascular lymphatics by neoplastic cells is a condition first noted by Andral [1] in 1829, again by Virchow [2] in 1855 and of which the gross lesions and the histopathology were described in detail by Troissier [3] and Raynaud [4] in 1874. It is most commonly secondary to carcinoma of the stomach, usually of the scirrhous infiltrating type, but primary sites in the bronchus and breast,[5] rectum,[6] kidney,[7, 8] ovary,[9] tongue,[10] prostate [11] and liver,[12] have been noted. The primary gastric malignancy is often clinically latent, or causes few symptoms, and the presenting complaints are those of respiratory or circulatory embarrassment. In some of the reported cases there has occurred bone marrow involvement with a clinical picture predominantly that of a blood dyscrasia. In others, typical Krukenberg tumors have been found and, in these, the primary clinical manifestations are often referable to the pelvis.

CASE REPORT

A colored male, aged 37, was admitted to the hospital with a complaint of left-sided chest pain, cough, hemoptysis and fever. The onset of the complaint was about three months before admission at which time there was noted a dull ache in the left thorax, which was exaggerated by coughing. Cough was not persistent until about three weeks before admission when it became severe, and was accompanied on each occasion by expectoration of about a teaspoonful of purulent material tinged with blood. Dyspnea on exertion appeared at about this time. During the previous two months there had been an evening rise in temperature. There had been considerable loss of weight. The past history was insignificant except for the presence of occasional gaseous distention and vague epigastric pain. Gonorrhea and syphilis had been contracted two years before admission.

Physical examination showed a well-developed, well-nourished, colored male with a blood pressure of 135 mm. of Hg systolic and 95 mm. of Hg diastolic, a pulse rate of 110 per minute and "a rapid rate of respiration." There was a scar on the right side of the neck said to have been caused by a "gland breaking down and draining from 1918 to 1924." There was lagging and limitation of motion of the left upper thorax. Fine râles, increased fremitus, and dullness on percussion were found in the left upper anterior and posterior portions of the chest. The rest of the physical examination was normal. The clinical impression was pulmonary tuberculosis versus pulmonary actinomycosis. The laboratory findings were as follows: Examinations of the sputum on eight different occasions, three of these being 24 hour concentrated specimens, were negative for acid fast organisms, nor were fungi found. Roentgenogram of the chest, on the day of admission, showed widely disseminated vesicular lesions in the middle areas of both lungs, and the left lower lung. The lesions were more or less discrete in the perihilar region, and in the left lower lung

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there was extensive lung reaction. It was thought that the changes were most likely due to actinomycosis or other mycotic infection, although the possibility of miliary carcinomatous metastases was mentioned.

An erect posterior-anterior roentgenogram the next day was interpreted as indicating tuberculous bronchopneumonia throughout both lungs. Approximately one month later a similar roentgenogram showed no further changes. Again, one month later (two months after the patient's admission) an erect posterior-anterior roentgenogram was taken and no change of the bilateral miliary disease was seen, but there was a complete clearing up of the large area of reaction in the left lower lung. It was here suggested that infestation with *Paragonimus westermanni* be considered, but sputum and stool examinations were negative for this parasite. The blood count of this time showed a hemoglobin of 30 per cent (Sahli), 8,000,000 red blood cells, of which many were immature forms, and a white cell total of 10,400. The differential count was normal. A blood Wassermann test was negative.

Course: The course was progressively down hill. The temperature ran a septic course, varying from 98° to 101° daily. The pulse rate changes were in accord with temperature changes and varied from 80 to 120 per minute. The respiratory rate, however, increased progressively from 20 per minute on admission to 45–50 per minute during the terminal weeks of the patient's illness. Fifteen days before the death of the patient, he raised about 50 c.c. of "Burgundy-red" fluid, which gave a strongly positive benzidine reaction, but was negative for organisms except spirochetes and streptococci. The dyspnea became so severe that morphine was required to relieve the distress during the terminal month. The patient died two and a half months after admission, five and a half months after onset of symptoms, and no final clinical diagnosis was made.

Autopsy: Necropsy was performed 72 hours after death. The external examination, except for emaciation, was negative. The peritoneal cavity and abdominal organs were normal in appearance and relationship except for prominent lymphatic channels over the peritoneal surface of the diaphragm, and enlarged lymph nodes along the lesser curvature of the stomach. In addition a large mass involving the stomach wall was palpated; it extended from over the cardiac end of the stomach down to within 3 cm. of the pyloric sphincter along the lesser curvature. The wall of the stomach, particularly in the region of the lesser curvature, was quite indurated in the cardiac one third. The left pleural cavity was completely obliterated over the lower lobe. The pleura over the left lower lobe was markedly thickened, white in color, and areas of calcification were present. The visceral pleura over the left upper lobe showed marked distention of the lymphatics. The visceral pleura over the entire right lung showed a similar lymphatic distention. The cut surface of the lungs showed dilated lymphatics along the bronchial and vascular trees. A few small areas of bronchopneumonia were scattered throughout. The bronchial mucosa was congested, and some of the bronchi contained a hemorrhagic, purulent material. The tracheobronchial lymph nodes were not enlarged but, on section, showed white miliary nodules. The pleural surface of the diaphragm showed dilated lymphatics similar to those seen on the peritoneal surface.

The peripancreatic lymph nodes were enlarged, and on section were firm and had a white color. On opening the stomach, a large ulcerated mass along the entire course of the lesser curvature was found. In the cardiac area the tumor was firm in consistency and scirrhous in nature, and the mucosa was absent over this area. In the pyloric region the mass was polypoid and gelatinous in appearance. Radiating from this tumor there were dilated lymphatics, with nodules interspersed along their courses. The capacity of the stomach did not appear to be lessened.

The periaortic lymph nodes were enlarged and some were caseous. The heart was normal except for dilatation of all chambers and moderate atherosclerosis of the

mitral and aortic valves. A small white nodule 3 mm. in diameter was found in a medullary pyramid of the right kidney. The liver, gall-bladder and duct system, spleen, pancreas, intestinal tract, kidneys, adrenals, ureters, urinary bladder, and genitalia were otherwise grossly normal.

Microscopic Examination

Lung: The pleura showed an increased amount of connective tissue. There was more or less reduction of the size of the blood vessels due to intimal proliferation. Many of the adjacent lymphatic channels were widely dilated by plugs of neoplastic cells. These cells were large, had a pale cytoplasm, basophilic nuclei, and many showed mitosis. The majority of the smaller arterioles throughout the entire lung section showed a similar involvement. Masses of these tumor cells were also seen in the blood vessels of the alveolar septa. An occasional arteriole showed a recanalization of a thrombus, and tumor cells were seen in the newly formed channels. The alveolar spaces showed in some places an accumulation of fibrin and a few round cells. Otherwise they were normal. The bronchiolar and bronchial mucosa was normal.

Stomach: The mucosa was replaced by atypical glandular tubules which penetrated through the muscularis mucosae to the submucosa. These tubules were lined by several layers of cells with large hyperchromatic nuclei, the cytoplasm of which was pale and the borders indistinct. There was some myxomatous degeneration of the connective tissue of the submucosal layers.

Diaphragm: The lymph channels of the section showed a distention by tumor cells similar to the process seen in the pleura. Otherwise no abnormalities were present.

Periaortic Lymph Node: The architecture of the node had been greatly distorted because of replacement of normal tissue by neoplastic cells. These were large, had a pale cytoplasm, and deeply stained nuclei. Some showed mitosis. The capsule was thickened but did not appear to be invaded.

The heart, liver, spleen, adrenal glands, kidneys, prostate, and the remainder of the intestinal tract showed no unusual findings.

Discussion

Because of the protean clinical manifestations, lymphangitic carcinomatosis of the lungs is usually diagnosed with more or less difficulty. In general it occurs most commonly in young adults—the great majority of cases occurring before the age of forty. As previously mentioned it is most frequently secondary to scirrhous carcinoma of the stomach. The primary gastric malignancy, which varies in size from a microscopic area [13, 14, 15] to one, as in the present case report, involving a large portion of the stomach, is often clinically latent or causes few symptoms,[16, 17, 18, 19, 20, 21] and the presenting complaints, as previously stated, are those of respiratory difficulty or circulatory embarrassment. The respiratory symptoms are rapidly progressing dyspnea with or without cyanosis,[5, 16] a slight cough, the expectoration of a thin brownish, sometimes purulent or sanguineous, sputum. There is a rapid downhill course.[22] The chest findings on examination are negative, or insignificant in proportion to the symptoms.[23, 24] The roentgen-ray findings are often times suggestive, but are not diagnostic. The characteristic appearance is a markedly stringed design in both lungs, which consists of branching lines which arise from the hilum and break up into a fine network as they extend toward the periphery, and at the

points of intersection miliary nodules may be seen. Frequently the hilar nodes are enlarged.[24, 25, 26, 27, 28] Right sided heart failure or asphyxia is not uncommonly the mode of exitus.[5, 17, 20, 29, 30, 31]

The gross pathologic findings in the lungs are characteristic if sufficiently marked, but in some cases the nature of the pulmonary involvement has not been

FIG. 1. Distention of subpleural lymphatics. (From Textbook of Pathology, by C. W. Duval and H. J. Schattenberg, page 517, 1939, D. Appleton-Century Co., New York.)

suspected until microscopic examination has revealed its identity.[5, 12, 14, 18, 21, 32, 33, 34, 35, 36, 37]

The lung is larger, firmer, and more moist than normal. There is a dilatation of the pleural lymphatic channels which causes them to stand out prominently, and the lobules of the lung are characteristically delineated. At the points of intersection of the lymphatic channels small yellowish white nodules may be seen (figure 1). On cut section the lung appears mottled and similar involvement of peribronchial and perivascular lymphatics is seen. Small plugs can be ex-

pressed sometimes from these involved vessels. Microscopically, tumor cells are found filling the perivascular, peribronchial, and pleural lymphatics (figures 2 and 3). In many cases, tumor cells are also found in the vessels of the alveolar walls (figure 4) and there is often noted an intimal proliferation, sometimes elliptical in nature,[29] which more or less occludes the arterioles (figure 5). Also there is occasionally thrombosis of a vessel with tumor cells present in the thrombus, and again recanalized thromboses are seen with tumor cells lying in the newly formed channels (figure 6).

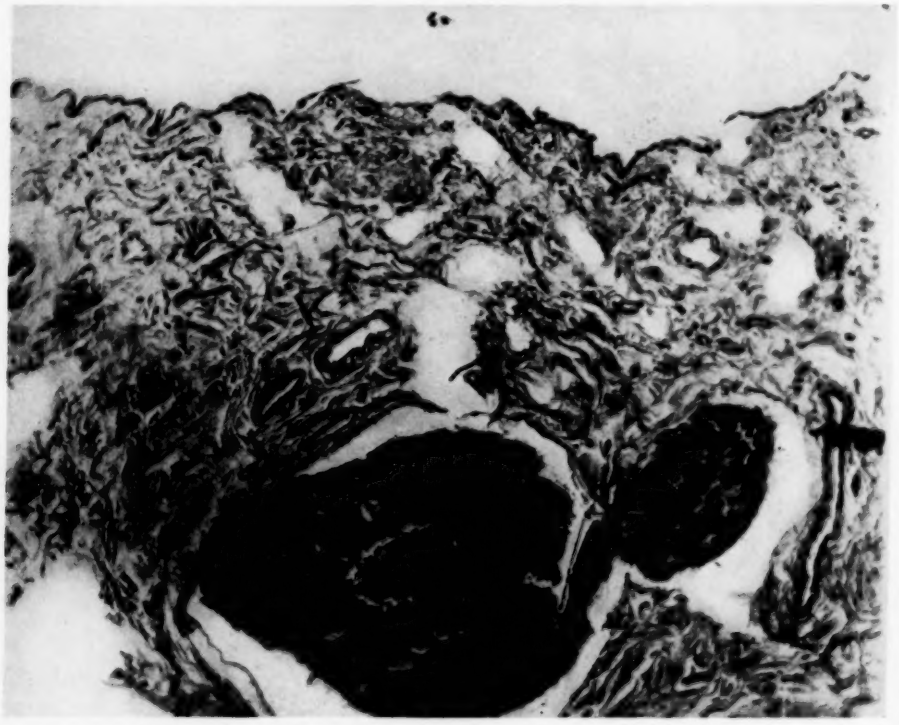

FIG. 2. Section of pleura showing tumor cells lying in a lymphatic channel. (× 100.)

The method of spread to the lung is, most probably, by retrograde lymphatic involvement, following lymphatic permeation [26, 38, 39, 40, 41, 42] but the frequency with which tumor cells are found distending the channels of alveolar walls demands another explanation, since these are definitely blood, and not lymph, vessels.[43] In a case reported by Turettini and Gerber [44] there was thrombosis of the superior vena cava, right internal jugular vein, and the right axillary vein. In a case reported by Boccard [30] there was thrombosis of the left basilic and saphenous veins. Chylous ascites was present in Gamberini's case [45] and in a case reported by Poppi [28] there was also chylous ascites, as well as thrombosis of the left subclavian vein. These observations support the possibility that the thoracic duct is involved, and tumor cells gain entrance to the venous circulation in this way.[37]

The presently described case is one in which the form of lymphangitic carcinomatosis is predominantly pulmonary in its clinical manifestations. There are several other ways in which a metastatic carcinoma infiltrating the pulmonary channels may first manifest itself. One of these is right-sided heart involvement. There is first hypertrophy and then dilatation. If dyspnea and cyanosis are also present, the condition may simulate Ayerza's disease. Montgomery [46] has suggested the use of the term "Ayerza's syndrome" and voices the opinion that while the clinical features are clear cut, the underlying pathological process may be quite different in individual cases.[47] The blockage of the pulmonary

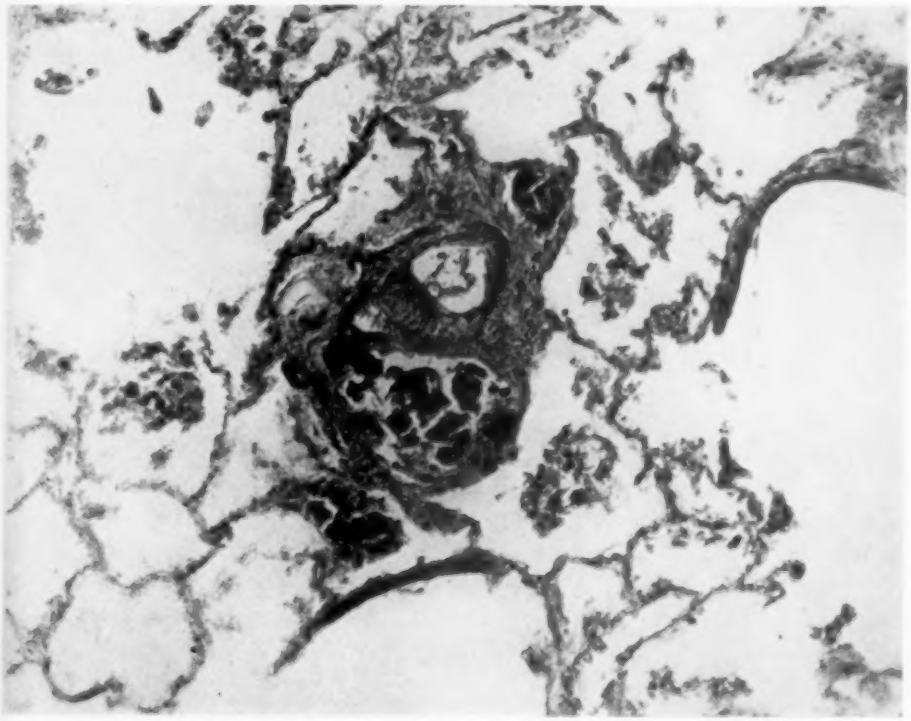

FIG. 3. The lymph channels adjacent to an arteriole are plugged by tumor cells. There is intimal proliferation of the arteriole. (× 440.)

circulation by the widespread intimal hyperplasia, arteriolar thromboses, and the further reduction of blood flow by the myriad tumor-cell emboli explains the hypertrophy of the right heart. The cyanosis and asphyxia are probably due to the reduction of pulmonary ventilating area,[48] although Porges, in discussing cases reported by Cérkake [23] attributed the dyspnea to stiffening of the lung by the carcinomatous infiltration of alveolar septa. Girode [40] believed that edema of the lung was the underlying factor. Von Meyenburg [39] felt that there was a cardiac element in his cases, and Goldmann [49] suggested that there was an intoxication of the nervous centers by the products of the neoplasm.

There have been a number of cases reported in which extensive bone marrow metastases were noted, as well as lymphatic infiltration of the lungs.[11, 12, 14, 32, 34,

[35, 36, 50, 51, 52] The predominant clinical features of these cases were those of a blood dyscrasia. The blood changes subsequent to cancerous involvement of the bone marrow are known in the French literature as the syndrome of Weil and Clerc [54] and the principal manifestation is a hemorrhagic diathesis. The next commonest change, excluding anemia, is the presence of immature leukocytes and erythrocytes in the peripheral blood. Curiously enough, in a number of cases reported of lymphangitic carcinomatosis, a thrombocytopenia has been

FIG. 4. Infiltration of blood channels of alveolar septa by tumor cells. (× 900.)

noted [11, 12, 14, 32, 34, 35, 52, 53] which is not in accord with the view that in carcinoma the platelets are normal, or increased in number in the circulating blood.[55, 56, 57] Because of the lack of other symptoms, certain of these cases have been diagnosed as pernicious anemia, purpura, or leukemia,[32, 35, 36] and an unsuspected lymphangitic carcinomatosis of the lungs secondary to a primary gastric malignancy was found at autopsy. The method of metastasis to the bone marrow is not as obvious as in the other related syndromes in which it is characteristically

lymphogenous. The consensus of opinion is that the bone marrow is not supplied with lymphatics, but certain experimental work [58] is suggestive of the presence of lymphatics in the bone marrow, and to be consistent in keeping with the tendency of this tumor to metastasize by the lymphogenous route, it might be expected that the bone marrow is thus involved.

Finally the high occurrence of the Krukenberg tumor in the reported cases of lymphangitic carcinomatosis of the lung may be of significance. The classical Krukenberg tumors of the ovary are now considered to be generally secondary to gastrointestinal carcinoma, and quite frequently secondary to gastric carcinoma.

Certain clinical features of Krukenberg tumor are interesting in connection

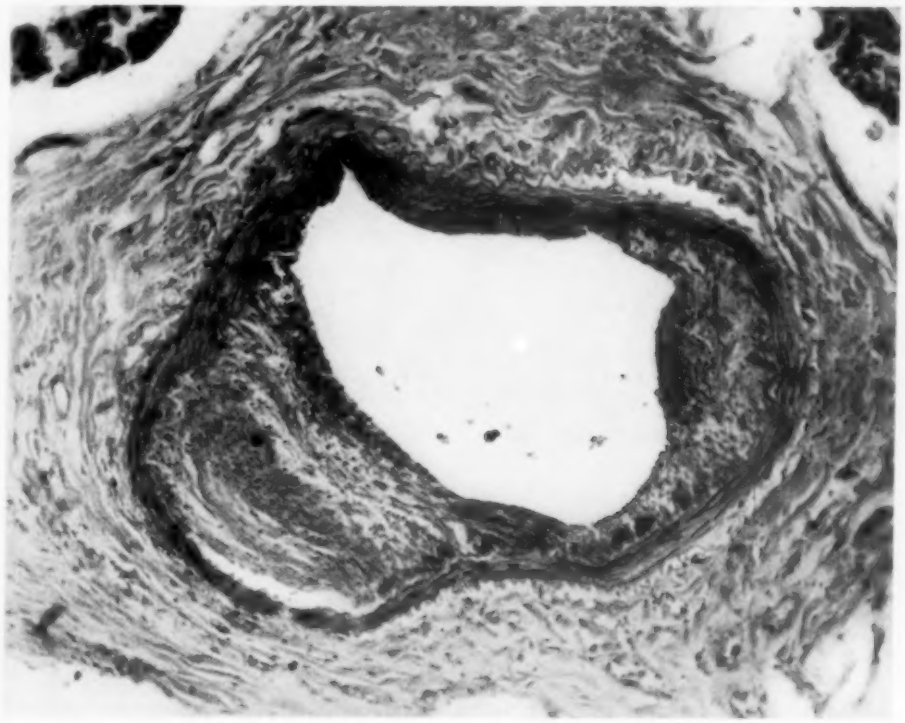

FIG. 5. Elliptical vascular intimal proliferation. (× 440.)

with the occurrence of lymphangitic carcinomatosis of the lung. Krukenberg tumors tend to occur in young adults, and also the primary carcinoma is often clinically latent. The average age for malignant tumors of the ovary, primary or secondary (excluding cystic teratoma and possible sarcoma) falls between 42 and 50 years.[59] The average age of occurrence of Krukenberg tumor is well under this.[60, 61, 62] The pelvic symptoms are frequently the first, and later developments of gastrointestinal, or pulmonary symptoms, follow, or the gastrointestinal involvement is an incidental finding at operation or autopsy.[63, 64, 19] Of interest is one report [65] of a patient operated upon successively for adenocarcinoma of the stomach and Krukenberg tumor of the ovary, who then developed lymphangitic carcinomatosis of the lungs.

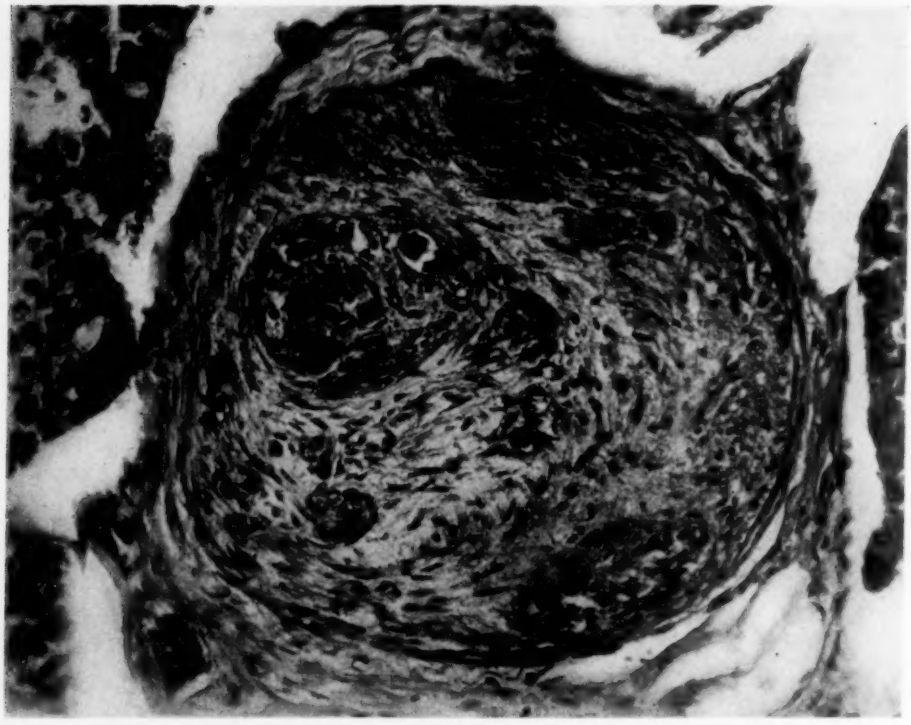

FIG. 6. Recanalized vessel with tumor cells in new channels. (× 900.)

SUMMARY

Lymphangitic carcinomatosis of the lungs is not an uncommon form of metastasis in gastrointestinal carcinoma, especially scirrhous carcinoma of the stomach, in young individuals.

The symptoms and signs due to the lung involvement may be similar to, and must be differentiated from, Ayerza's syndrome, pulmonary tuberculosis, pulmonary fungus infection or pulmonary infestation by *Paragonimus westermanni*.

Certain blood dyscrasias are noted at times in connection with lymphangitic carcinomatosis of the lungs and these may be due to metastatic involvement of the bone marrow.

A significant incidence of Krukenberg tumor of the ovary has been noted in cases of lymphangitic carcinomatosis of the lungs.

The signs and symptoms caused by the metastatic foci often overshadow those of the primary lesion, or the primary lesion may be clinically latent.

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EDITORIAL

THE AMERICAN COLLEGE OF PHYSICIANS AND MEDICAL DEFENSE

IN THE Defense Program in which this Nation is engaged, a heavy responsibility falls upon the medical profession. The efficiency of the Army and of the Navy in this period of rapid growth depends to a marked degree upon the careful selection of those young men best fitted by physique and mentality to meet the requirements of active service in war. It depends equally upon the maintenance in vigorous health of those already inducted who in camps and at sea are being moulded into a force prepared to meet any challenge. These young soldiers and sailors and aviators, so history teaches us, if it were not for modern medical care would suffer in this training period a rate of disability and death from disease quite comparable to the casualty rate in active combat. To safeguard our growing defense forces involves a major medical program which both in its planning and in its execution calls for the services of the ablest men in the medical profession. Moreover since the medical personnel which will serve these new military forces must be drawn to a great extent from the ranks of medical men now in civilian practice it is necessary that they be so selected as not to reduce the number of practitioners in any area below the minimum required to meet the civilian needs for medical care. Our rural and urban districts must retain a sufficient number of physicians, our hospitals and dispensaries must continue to function, and our medical schools must be able to ensure a continuing flow of well-trained young graduates. It must be expected that when the Army and Navy have taken their quota, the remaining physicians will bear their share of the burden of adequate defense through the longer hours of work that will be required of them.

The profession as a whole then will be called to the service of the nation as it has been in all past war emergencies. No group will fail to do its share. Each, however, has the right to take pride in the part played by its members.

It is for this reason and to make some record, partial though it must be, of what part members of the American College of Physicians are taking in this present phase of the Defense Program that this brief summary is presented.

In the regular Medical Corps of both the Army and Navy the American College of Physicians has many members and both Surgeon General Magee of the Army and Surgeon General McIntire of the Navy, as well as Surgeon General Parran of the Public Health Service, are Fellows of the College.

An unknown but large number of the members of the College are officers of the Medical Reserve Corps. Many of these are now being called into active service chiefly to man the medical divisions of cantonment hospitals. Many other members have joined the Reserve to aid in filling medical divi-

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sions of General Hospitals now being organized by Medical Schools for service in case of war.

Another large unlisted group of College members have accepted appointment and are hard at work on local Draft Boards, Advisory Boards and Induction Boards. Aside from those called into active service no other physicians have taken on such onerous duties for their country's defense as these men and all other physicians on these Boards.

The College is proud too of those of its membership who, working under the aegis of the Committee of Medical Preparedness of the American Medical Association, are engaged in every state in the difficult task of assisting the Army in the selection of medical officers in a way which will least affect the efficiency of medical practice, medical institutions and medical schools.

Likewise our members have been called to assist in the medical aspects of the work of the State Defense Councils.

Early in the development of the Defense Program the Surgeons General of the Army and Navy called upon the National Research Council to mobilize through its Division of Medical Sciences authoritative medical advice for the Medical Corps in purely professional subjects. The way in which this task has been performed is graphically shown in the adjoining chart.* It must prove a source of gratification to all the College to note how many of its Fellows have been honored by inclusion in these advisory bodies. As a result of the work of these Committees many research projects are underway, manuals are being written and far-reaching plans worked out to meet future possible eventualities.

In this connection the Regents of the College took official action in December in making available an emergency fund to the Executive Committee from which the Medical Committee of the National Research Council might obtain financial help for an urgent need which could not be met through the slow process of a special governmental appropriation. This fund stands as an evidence of the attitude of the College which was expressed by President Bruce when last fall he formally offered to the Government the services of the American College of Physicians in the Defense Program. As individuals and as a College our members have a right to pride in the part they have already played. The future shall not find us lacking.

* Since this organization is in process of growth, omissions or minor errors may be present in the chart.

REVIEWS

The Practitioner's Library of Medicine and Surgery. Supervising Editor, GEORGE BLUMER, M.A. (Yale), M.D. David P. Smith Clinical Professor of Medicine, Yale University School of Medicine; Consulting Physician to the New Haven Hospital. 1940 Supplement. xxxvii + 771 pages; 25 × 17.5 cm. D. Appleton-Century Company, Inc., New York. 1941. Price, $10.00.

As they have appeared in the interval between 1932 and 1938, the thirteen preceding volumes of *The Practitioner's Library of Medicine and Surgery* have been briefly described in the ANNALS. In order to keep this work abreast of the recent significant advances in Medicine a *1940 Supplement* has been published. In its 64 chapters by almost as many authors, new disease entities are discussed and new diagnostic and therapeutic technics are described. The arrangement of the chapters in this volume follows in general that of the *Library* as a whole. Among the topics presented are the medical applications of neutron rays and artificial radioactivity, the modern hypothesis and the clinical aspects of the menstrual cycle, the pneumococcus, diagnostic roentgenology with special reference to the newer technics, technic and indications for the use of gastroduodenal aspiration, equine encephalitis, acute interstitial pneumonia, rickettsioses, epulis granulomatosa, acute disseminated lupus erythematosus, torulosis, toxoplasmic encephalomyelitis, histoplasmosis of Darling, tick paralysis, marihuana addiction, endemic dental fluorosis, cardiac contusion, leukemoid reactions, sulfanilamide and allied drugs, chemotherapy of gonococcal infections, the treatment of meningococcal infections and of lymphogranuloma venereum, gold therapy in chronic arthritis, indications for the use of vitamin K, the vitamin B deficiencies, the treatment of myasthenia gravis, dilantin sodium in epilepsy, recent progress in ophthalmology and in otology, and the end results of the toxemias of pregnancy. Other chapters, which cannot be listed here, cover material of equal interest and value. On the whole, the choice of subject material seems to be excellent. Obviously no attempt can be made to review the material of the individual articles in a collected work of this nature. There is a separate index as well as a detailed table of contents. The style and binding are uniform with those of the earlier volumes. As a well-planned addition to the *Library*, the *1940 Supplement* will be welcomed by all who use this medical encyclopedia.

C. V. W.

A Text-Book of Psychiatry. By D. K. HENDERSON, M.D., and R. D. GILLESPIE, M.D. Fifth Edition. 660 pages; 22.5 × 14.5 cm. Oxford University Press, London: Humphrey Milford. 1940. Price, $6.00.

Since the first edition of this textbook was published in 1927, serious students of psychiatry have been indebted to these authors for the scholarly way in which the subject matter has been presented. The subsequent editions have lost none of this but rather have added timely, new material at the same high level.

The present edition is especially to be welcomed for certain important additions and changes. Particularly to be commended is the well balanced, critical presentation of the various shock therapies, together with a fair evaluation of their merits and disadvantages. The discussion of Gjessing's investigations of metabolic differences among the stuporous patients is also of interest.

The "boldness" of the authors in separating the psychopathic states from the mental defectives seems to be only in line with the present-day American trends. In the text it is more than justified by the result, for this section of the book is handled

much better than in earlier editions. The chapter on the psychiatry of childhood has benefited greatly by the additional material.

In general it may be said that, with the exception of what seems to the reviewer somewhat inadequate presentations on the subjects of electro-encephalography, details of the technic of the treatment of general paresis, and the clinical management of alcoholic intoxications, this text gives a highly satisfactory survey of the field of psychiatry. In no other text are the varied and at times conflicting theories discussed with so little bias. The authors let the various sources speak for themselves and the quotations and condensations from the literature are accurate.

The reviewer considers this the textbook of preference for serious students of psychiatry and psychiatrists.

L. F. W.

The Head and Neck in Roentgen Diagnosis. By HENRY K. PANCOAST, M.D., EUGENE P. PENDERGRASS, M.D., and J. PARSONS SCHAEFFER, M.D., PH.D. 976 pages; 26 × 18 cm. Charles C. Thomas, Springfield, Illinois. 1940. Price, $12.50.

This is a one volume publication intended primarily for the roentgenologist; it covers thoroughly roentgenology of the head and neck. It is well printed and contains 1251 illustrations, the reproductions of the roentgen-ray films being of the best quality. A complete bibliography is appended which is a very valuable feature. An excellent subject index is likewise provided. Clearness and orderliness throughout the text are to be commended. In the preface the authors state "in order that maximal results in medical and surgical diagnosis by means of the roentgen-rays may be obtained, the basic and technical aspects of radiology must be correlated and integrated intimately with developmental and adult morphology, physiology, pathology and observations in clinical medicine and surgery and the special branches." This they have accomplished exceptionally well.

This book is divided into 12 chapters. The first chapter is devoted to the anatomy of the skull principally as seen radiographically with due attention given to the related structures and development. Variations and anomalies are considered in the general discussion as well as in a special section where they are described more fully. Chapter 2 deals with fractures of the skull and cervical spine. Fractures of the facial bones are considered individually. Great stress is placed upon doing a complete examination. The technic required to best demonstrate lesions is discussed.

Diseases of the bones (skull and cervical spine) and tumors of the scalp and cervical spine are described at length in chapters 3 and 4. Chapter 5 is devoted entirely to the teeth and jaws. The nose, lacrimal passage-ways, paranasal sinuses and temporal bones with special reference to the mastoids and petrous portions receive equal consideration in chapters 6 and 7.

There is an excellent chapter on intraorbital and intraocular foreign bodies. The authors describe the structural aspects of the eyeball in detail followed by the various roentgenographic methods of localization of foreign bodies. The modified Sweet method is discussed thoroughly.

Two especially interesting chapters are devoted to intracranial tumors and cerebral pneumography. The remainder of the book is taken up with chapters giving in detail roentgenographical diagnosis as applied to the neck.

This is an excellent and practical book which should be in the hands of every roentgenologist.

H. J. W.

Physical Diagnosis. By RALPH H. MAJOR, M.D. 464 pages; 24.5 × 16 cm. W. B. Saunders Co., Philadelphia. 1940. Price, $5.00.

This is an interesting but somewhat disappointing textbook, couched in a moderately classical style with many Greek derivations and much historical lore.

After an interesting chapter on pain and the usual stressing of routine, there are excellent discussions of physical diagnosis as applied to the cardiovascular and respiratory systems. Other chapters are less adequate.

There is an abundance of pictures, many of them so extreme as to suggest Gould and Pyle rather than anything to be met with in ordinary student experience. None of the illustrations are in color, and where black and white photographs are used in an attempt to show comparison of color, as in Addison's disease, the effort is not felicitous. Diagrams and schematic presentations where used are very helpful and should be used more.

The rather general omission of vitamins in physical diagnosis is striking. Pellagra is mentioned, and scurvy, but so many of the other vitamin manifestations are omitted as to give the reviewer a feeling that they have been ignored entirely.

Occasional dicta are misleading, as where loss of hair and furrowing in the nails are ascribed specifically to typhoid fever instead of being part of many febrile and trophic disturbances. Coilonychia is beautifully illustrated, but ascribed entirely to pernicious anemia, instead of hypochromic anemias. Rhagades is attributed exclusively to syphilis, with no mention of the fact that it occurs in people who do not wear their dentures well. Elevation of temperature is described as characteristic of hemorrhage, without mention of time relation or whether the hemorrhage is internal or external.

The textbook has many good points, but because of the general lacks mentioned above is rather disappointing.

C. A.

Selected Writings of Sir Charles Sherrington. Compiled and edited by D. DENNY-BROWN. xiv plus 532 pages, with 85 diagrams; 26 × 18.5 cm. Paul B. Hoeber, Inc., New York. 1940. Price, $7.50.

This book is comprised of extracts and reprints of many of the papers of Sir Charles Sherrington, and is a worthy tribute to his genius and versatility. The papers are not arranged chronologically but according to subject matter. The author has divided the book into 11 chapters which deal with the distribution of motor and sensory nerve roots, sensory nerves to muscles, the spinal animal and the nature of spinal reflex activity, features of spinal and bulbar reflexes, the anatomical course of reflex connections in the spinal cord, reciprocal innervation, postural reflexes, the motor area of the cerebral cortex, the nature of excitation and inhibition, and the quantitative management of contraction in lowest level coördination.

The book has a particular value from the arrangement of the material which has been well handled and illustrated, and it will be particularly useful as a reference book to the neurologist and physiologist.

A complete bibliography of Sir Charles Sherrington's writings is appended.

E. F. C.

COLLEGE NEWS NOTES

New Life Members of the College

The following Fellows of the American College of Physicians have subscribed to Life Membership, and their initiation fees and Life Membership subscriptions have been added to the permanent Endowment Fund of the College:

Dr. Harry L. Arnold, Honolulu, T. H.
Dr. Paul W. Clough, Baltimore, Md.
Dr. Eugene Henry Drake, Portland, Maine
Dr. C. J. Fishman, Oklahoma City, Okla.
Dr. Russell Richardson, Philadelphia, Pa.
Dr. E. Sanborn Smith, Kirksville, Mo.
Dr. Edward L. Whitney, Walla Walla, Wash.
Dr. John R. Williams, Rochester, N. Y.

Gifts to the College Library

We gratefully acknowledge receipt of the following gifts donated to the College Library of Publications by Members:

Books

Dr. Jacob Gutman, F.A.C.P., Brooklyn, N. Y.—1st Supplement to "Modern Drug Encyclopedia and Therapeutic Guide," 2nd edition;
Dr. Alpheus F. Jennings, F.A.C.P., Detroit, Mich.—"Typhoid Fever," reprinted from Tice's Practice of Medicine, Volume IV;
Dr. Solomon Solis-Cohen, F.A.C.P., Philadelphia, Pa.—"Judaism and Science";
Dr. J. Russell Twiss, F.A.C.P., New York, N. Y.—"Diagnosis and Management of Diseases of the Biliary Tract."

Reprints

Dr. J. Graham Bruce (Associate), Springfield, Mass.—1 reprint;
Rear Admr. Charles S. Butler, F.A.C.P., (MC), U.S.N., Retired, Bristol, Tenn.—1 reprint;
Dr. Hugh R. Butt, F.A.C.P., Rochester, Minn.—1 reprint;
Dr. J. William Finch (Associate), Hobart, Okla.—2 reprints;
Dr. Max L. Garon, F.A.C.P., Louisville, Ky.—1 reprint;
Dr. Vincent W. Koch, F.A.C.P., Janesville, Wis.—1 reprint;
Dr. William G. Leaman, Jr., F.A.C.P., Philadelphia, Pa.—1 reprint;
Dr. Willard Machle (Associate), Cincinnati, Ohio—2 reprints;
Dr. Charles F. Nichols, F.A.C.P., Philadelphia, Pa.—2 reprints;
Dr. Dwight O'Hara, F.A.C.P., Boston, Mass.—1 reprint;
Dr. Robert C. Page (Associate), Mount Vernon, N. Y.—2 reprints;
Dr. Zolton T. Wirtschafter (Associate), Cleveland, Ohio—2 reprints.

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American Board of Internal Medicine: William S. Middleton, M.D., Secretary 1301 University Ave. Madison, Wis.	Oral Examination, Boston, April, 1941, in connection with meeting of the American College of Physicians. Oral Examination, Cleveland, June, 1941, in connection with meeting of the American Medical Association. Written Examination, October 20, 1941. Final date for filing application is September 1, 1941.
American Board of Pathology: F. W. Hartman, M.D., Secretary Henry Ford Hospital Detroit, Mich.	Cleveland, June 2–3, 1941, in connection with the meeting of the American Medical Association. Final date for filing application is May 1, 1941.
American Board of Pediatrics: C. A. Aldrich, M.D., Secretary 707 Fullerton Ave. Chicago, Ill.	New York City, March 30–31, 1941, immediately following the Region I meeting of the American Academy of Pediatrics. Chicago, May 18, 1941, immediately following the Region III meeting of the American Academy of Pediatrics. Boston, October 12, 1941, immediately following the annual meeting of the American Academy of Pediatrics.
American Board of Radiology: B. R. Kirklin, M.D., Secretary 102 Second Ave., S. W. Rochester, Minn.	Oral Examination, Cleveland, May 30–June 1, 1941, in connection with the meeting of the American Medical Association. Final date for filing application is April 15, 1941.

Regional Meeting, Fellows and Associates of Eastern Pennsylvania

Under the governorship of Governor Edward L. Bortz, the "Third Annual Round-Up" of Fellows and Associates of the American College of Physicians from Eastern Pennsylvania was held in Philadelphia, Friday, February 7, 1941. In addition to the members from Eastern Pennsylvania, Fellows and Associates from Delaware and southern New Jersey were invited, and several members from the western Pennsylvania district also were present. More than 200 members were in attendance.

The meeting started with a buffet luncheon at the College home, 4200 Pine Street, at one o'clock p.m. It was followed by a scientific program in the Clinical Amphitheater of Jefferson Medical College, as follows:

1. Clinic: "Viruses."
   Dr. Hobart A. Reimann, Professor of Medicine, Jefferson Medical College, Philadelphia.
2. "Gonadal Hormones."
   Dr. Roland Klemmer, Chief of Medical Service, Lancaster General Hospital, Lancaster.

3. "Emotional Growth."
   DR. FRANCIS J. BRACELAND, Associate Professor of Clinical Psychiatry, Woman's Medical College; Assistant Professor of Psychiatry, University of Pennsylvania Graduate School of Medicine.
4. "Atelectasis."
   DR. DONALD R. FERGUSON, Clinical Professor of Medicine and Visiting Physician, Hahnemann Medical College and Hospital.
5. "Arterial Hypotension."
   DR. THOMAS M. DURANT, Associate Professor of Internal Medicine, Temple University School of Medicine.
6. Clinic: "Modern Therapy."
   DR. HENRY K. MOHLER, Dean and Prevost Professor of Therapeutics, Jefferson Medical College.

The evening was given over to dinner and social activities. Dr. George Morris Piersol, Secretary-General, and former President of the College, was the toastmaster. Among special guests were the following College Governors: Dr. Charles F. Tenney, Governor for Eastern New York; Dr. Lewis B. Flinn, Governor for Delaware; Dr. Louis Krause, Governor for Maryland; Dr. Alex. M. Burgess, Governor for Rhode Island. Among other guests at the Speakers' Table were: Dr. Sidney R. Miller, Baltimore, former President of the College; Dr. Hubley R. Owen, Director of Public Health of Philadelphia; Dr. Margaret D. Craighill, Dean of the Woman's Medical College of Pennsylvania; Dr. William A. Pearson, Dean of Hahnemann Medical College of Philadelphia; Dr. Hobart A. Reimann, Professor of Medicine at Jefferson Medical College; Dr. George Muller, Philadelphia, former President of the American College of Surgeons; Dr. F. F. Borzell, President of the Medical Society of the State of Pennsylvania; Dr. O. H. Perry Pepper, Philadelphia, former President of the College; and Mr. E. R. Loveland, Executive Secretary of the College.

Dr. Pepper gave an address on the activities of the Committee on Medicine of the National Research Council, of which he is the Chairman, and of which the personnel is made up completely of Fellows of the College. The Committee on Medicine is conducting an important work in medical national defense, in an advisory capacity with the Surgeons-General of the Army and Navy. The Executive Secretary, Mr. Loveland, reviewed the progress of the College during the past fifteen years, and discussed the program of the forthcoming Annual Session of the College in Boston. Dr. Bortz made some remarks as the College Governor, but devoted most of his address to a discussion of the program of Postgraduate Courses for the current year, Dr. Bortz being the Chairman of the Advisory Committee on Postgraduate Courses. He pointed out that the registration to February 7 for the 1941 Courses, although many courses were not scheduled to start for six weeks thereafter, already had excelled the total registration of any preceding year. He especially commended to the physicians present Postgraduate Course No. 10, Military Medicine, arranged through the Public Services of the United States at Washington, April 7–18.

Short addresses were made or greetings extended by the other guests. Dr. Harry Wilmer, F.A.C.P., Philadelphia, and a number of his fellow members of the Orpheus Club of Philadelphia, enlivened the program with new songs and famous melodies.

Each year these Regional Meetings for Eastern Pennsylvania are growing in size and with enthusiasm among the members. Governor Bortz and a very active Governor's Committee deserve commendation and real recognition for the success of these meetings.

REGIONAL MEETING OF MONTANA MEMBERS OF THE COLLEGE

The Montana Branch of the American College of Physicians held their meeting at Billings, Mont., on February 15, 1941. The program began at 2:00 p.m. with case

reports and presentation of patients by Dr. Robert W. Currie (Associate) and Dr. Wayne Gordon, F.A.C.P., Billings, and by Dr. Meredith B. Hesdorffer (Associate), Missoula. Following the afternoon session the business session was held with dinner at 7:00 p.m. In the evening Dr. M. A. Shillington, F.A.C.P., Glendive, presented a study on "The Treatment of Hay Fever," followed by Dr. Charles F. Little (Associate), Great Falls, on "Chronic Obstruction of the Small Bowel." Fourteen members from over the state were present. Sessions were presided over by Dr. Ernest D. Hitchcock, F.A.C.P., College Governor for Montana.

Dr. O. H. Perry Pepper, F.A.C.P., Professor of Medicine at the University of Pennsylvania School of Medicine, Philadelphia, Pa., and Dr. Francis G. Blake, F.A.C.P., Professor of Medicine at Yale University School of Medicine, New Haven, Conn., have been appointed members of a four-man board to investigate, prevent, and control infectious diseases in the Nation's expanding armed forces by Secretary of War Henry L. Stimson.

The Tennessee State Medical Association has appointed the following Fellows of the American College of Physicians to its Committee on Postgraduate Instruction in Internal Medicine: Dr. J. Owsley Manier and Dr. Rudolph H. Kampmeier, Nashville, Dr. Franklin B. Bogart, Chattanooga, Dr. William C. Chaney, Memphis, and Dr. Robert B. Wood, Knoxville.

The 37th Annual Congress on Medical Education and Licensure was held in Chicago, Ill., February 17–18, 1941. Among the speakers at this meeting were:

Dr. C. Sidney Burwell, F.A.C.P., Dean, Harvard Medical School, Boston, Mass.—"A School of Dental Medicine";

Dr. Edward L. Turner, F.A.C.P., Meharry Medical College, Nashville, Tenn.—"Undergraduate and Graduate Medical Education for Negroes";

Dr. Reginald Fitz, F.A.C.P., Member, Council on Medical Education and Hospitals, American Medical Association, Boston, Mass.—"The Confused State of the Hospital Internship."

On March 13, 1941, Dr. Edward A. Strecker, F.A.C.P., Philadelphia, Pa., addressed a joint meeting of the Cape May County Medical and Bar Associations at Ocean City, N. J.

Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., has been appointed Chairman of the Committee on Nutrition of the Medical Society of the State of Pennsylvania. This is a newly formed committee and its projected plan will include the dissemination of the newer knowledge of nutrition—causes, prevention, early recognition and the medical management of nutritional deficiency.

Dr. Kelly was guest lecturer on the subject of "Calcium Metabolism and Its Abnormalities," before the Senior Class of the Woman's Medical College of Pennsylvania, January 24, 1941.

The New Jersey Gastroenterological Society will hold its Clinical Report Night and meeting at the Elizabeth General Hospital, Elizabeth, N. J., April 7, 1941. Among those who will participate in the program are: Dr. Sigurd W. Johnsen, F.A.C.P., Passaic, N. J., Dr. Hyman I. Goldstein (Associate), Camden, N. J., Dr. Manfred Kraemer, F.A.C.P, Newark, N. J., and Dr. Louis L. Perkel, F.A.C.P., Jersey City, N. J.

The National Gastroenterological Association will hold its 6th Annual Convention in New York, N. Y., May 13–16, 1941, under the presidency of Dr. Anthony Bassler, F.A.C.P., New York, N. Y.

Dr. Sigurd W. Johnsen, F.A.C.P., Passaic, N. J., and Dr. Hyman I. Goldstein (Associate), Camden, N. J., are the delegates of the New Jersey Gastroenterological Society to the National Gastroenterological Association.

Dr. Walter C. Alvarez, F.A.C.P., Rochester, Minn., spoke on "Abdominal Pain" at a recent meeting of the San Francisco County Medical Society, San Francisco, Calif.

Dr. Robert T. Lucas, F.A.C.P., Shreveport, La., was recently elected Vice President from Louisiana of the Tri-State Medical Society of Texas, Louisiana and Arkansas.

Dr. Joseph O. Weilbaecher, Jr. (Associate), has been appointed Acting Director of Charity Hospital, New Orleans, La.

Dr. George Erick Bell, F.A.C.P., Wilson, N. C., has been elected one of the Vice Presidents of the Seaboard Medical Association.

Dr. James P. Rousseau, F.A.C.P., has been appointed Professor of Radiology at the new Bowman Gray School of Medicine of Wake Forest College in Winston-Salem, N. C.

Dr. Arlie R. Barnes, F.A.C.P., Rochester, Minn., has been elected Vice President, and Dr. Carl V. Moore (Associate), St. Louis, Mo., Secretary-Treasurer, of the Central Society for Clinical Research.

Recently Dr. Cyrus C. Sturgis, F.A.C.P., Professor of Internal Medicine at the University of Michigan Medical School, Ann Arbor, delivered the Henry Sewall Memorial Lectures at the University of Colorado School of Medicine in Denver. He spoke on "The Therapeutic Value of Blood and Blood Substitutes" and "The Hemorrhagic Diseases."

Dr. Russell L. Haden, F.A.C.P., Cleveland, Ohio, spoke on "Treatment of Pernicious Anemia" at the annual clinic day, January 29, 1941, of the Mount Carmel Mercy Hospital at Detroit, Mich.

Commander John R. Poppen, F.A.C.P., (MC), U.S.N., Bureau of Aeronautics, was one of the lecturers at the 7th annual postgraduate course in ophthalmology and otolaryngology conducted recently at the University of Virginia Department of Medicine, Charlottesville, Va.

Among the guest speakers at the 56th annual session of the Mid-South Post Graduate Assembly held in Memphis, Tenn., February 11–14, 1941, were:

Major General James C. Magee, F.A.C.P., (MC), U.S.A., Washington, D. C.—"Medical Preparation for the Present Emergency";

Dr. William D. Stroud, F.A.C.P., Philadelphia, Pa.—"Digitalis, Its Indications and Best Method of Administration";

Dr. Elmer L. Sevringhaus, F.A.C.P., Madison, Wis.—"Obesity, Types and Treatment."

Dr. Charles H. Lutterloh, F.A.C.P., Hot Springs National Park, Ark., was named President-Elect of the society at this meeting.

Dr. Ernest L. MacQuiddy, F.A.C.P., Omaha, Nebr., has been named Associate Professor of Internal Medicine at the University of Nebraska College of Medicine, Omaha.

Dr. John H. Skavlem, F.A.C.P., and Dr. Leon Schiff, F.A.C.P., have been made Associate Professors of Medicine at the University of Cincinnati College of Medicine.

Dr. James B. Herrick, M.A.C.P., Chicago, Ill., delivered the Fifth Christian Fenger Lecture of the Institute of Medicine of Chicago and the Chicago Pathological Society on February 10, 1941. Dr. Herrick spoke on "Christian Fenger as I Knew Him, 1885–1902: A Study in Personality."

Dr. Mark Gerstle, Jr., F.A.C.P., has been promoted to Lieutenant Commander in the Medical Corps of the U. S. Naval Reserve and is on active duty as a neuropsychiatrist at the U. S. Naval Training Station, San Diego, California.

Dr. Anthony Bassler, F.A.C.P., LL.D., presented a paper on "Recent Advances in Gastroenterology" at a meeting of the Philadelphia chapter of the National Gastroenterologic Association, January 16, 1941. Before the Mid-Hudson chapter of the Montclair Medical Society, February 15, he read "The Intestine and Chronic Arthritis." "Pathologic and Clinical Aspects of Gall-Bladder Disease" was presented at the Academy of Medicine at Buffalo, February 26. He gave an address over WABC on the subject of "Dieting for Indigestion" for the New York Academy of Medicine, February 1.

OBITUARY

DR. FRANCIS EDWARD STEWART

Dr. Francis Edward Stewart, F.A.C.P., born in 1853, died February 21, 1941 at his home in Greene Manor Apartments, Greene and Johnson Streets, Germantown, Philadelphia, after a two months' illness. He is survived by two daughters, Mrs. Gilbert M. Tucker, Albany, and Miss Marjorie Mathews Stewart.

Dr. Stewart was a Graduate in Pharmacy from the Philadelphia College of Pharmacy in 1876, from where he also obtained his Master in Pharmacy. He became a Doctor of Medicine from Jefferson Medical College in 1879.

Some of the honors and degrees which Dr. Stewart enjoyed were: Fellow of the American Medical Association; Fellow of the American College of Physicians; Fellow of the American Academy of Medicine, June 9, 1916; Fellow of the American Therapeutic Society, being also one of its founders in 1900, and Chairman of its Committee on Organization. He was a life member and Honorary President of the American Pharmaceutical Association and Chairman of its Committee on Patents and Trademarks. Honorary life member of the American Medical Editors and Authors Association; honorary life member of the Pennsylvania Pharmaceutical Association.

Dr. Stewart also claimed distinction as a teacher, being associated with such renowned colleges as the Medico-Chirurgical College of Philadelphia, where he was Professor of Materia Medica, Botany and Physiology; Jefferson Medical College, where he was a Demonstrator and Lecturer on Materia Medica and Pharmacy; Women's Medical College of Pennsylvania and the Philadelphia College of Pharmacy where he was quiz master in Pharmacy and Chemistry.

In addition to the tasks already imposed upon him by the preceding facts, Dr. Stewart was also Associate Editor of the Therapeutic Gazette (1882). He was instrumental in selecting Professor Horatio C. Wood and Robert Mead Smith as editors in 1884–5 and transferring the editorial and publication headquarters to Philadelphia. He was associate editor also of the Medical Bulletin. Dr. Stewart was founder and director of the Scientific Department of Parke, Davis and Co., and his contributions to Frederick Stearns and Co., and the H. K. Mulford Co. are well known. His book "Stewart's Compend of Pharmacy" holds a place of esteem in the Pharmaceutical literary field.

Dr. Stewart has been a Fellow in the American College of Physicians since 1918 and never has his loyalty and interest waned. His death ends the career of a brilliant and gentlemanly scholar.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

BOSTON SYMPHONY CONCERT FOR MEMBERS AND FRIENDS OF THE COLLEGE DURING BOSTON SESSION

(Tuesday Evening, April 22, 1941)

Dr. Serge Koussevitzky, Conductor of the Boston Symphony Orchestra, has invited members and friends of the College to a concert at Symphony Hall, Massachusetts and Huntington Avenues, on Tuesday evening, April 22, during the Twenty-Fifth Annual Session of the College in Boston. Guests are requested to come at 8:45, in ample time before the doors close at 9:00 p.m. Tickets will be distributed free at the Hotel Statler on Monday and Tuesday, April 21 and 22. An opportunity to reserve seats ahead of time is also afforded to members who shall communicate with the Executive Secretary of the College.

The Boston Symphony Orchestra is noted for its superb performances, its preeminence, the vision and pertinacity of its leader, and its remarkable personnel. Henry L. Higginson assembled sixty players under the present name more than sixty years ago. Mr. Higginson's dreams were unique mainly in the strength of conviction which lay behind them, and the ability to produce tangible results. It was the response they aroused in fellow New Englanders which made the growth of the Boston Symphony Orchestra possible. It is said that Boston citizens of 1881 waited all night in a queue for their first season tickets, which showed a trait traceable to the earlier New England which strove for music while it was yet eclipsed by the literary arts. The trait can be described as the determination to experience beauty at its highest. It persists in the audiences of today who treasure their weekly concerts as their main source of musical renewal and growth.

George Henschel, from England, was the first conductor, serving until 1884. The second conductor was Wilhelm Gericke who served from 1884 to 1889, succeeded by Arthur Nikisch from 1889 to 1893. Mr. Gericke returned in 1898, serving until 1906, being succeeded by Karl Muck who conducted the Orchestra from 1906 to 1908 and from 1912 to 1918. In the spring of 1918, Mr. Higginson, the founder, who had now passed his eightieth year, was ready to relinquish what had become through external circumstances a heavy burden. He had given America an illustrious example of what symphonic performance could be. That accomplishment, the act of one man carried through thirty-seven years, has had no counterpart.

Judge Frederick P. Cabot, president of a board of trustees, assumed responsibility for the orchestra. In response to appeals from Judge Cabot and his associates, a relatively small number began, and individuals since that time have continued, to contribute towards its maintenance. The organization of the society of the Friends of the Orchestra has placed that charge in the hands of a large and growing portion of those who attend the concerts and consider them indispensable.

Serge Koussevitzky, the present conductor, before coming to Boston, had organized and conducted an orchestra in Moscow and St. Petersburg. He was accounted a leader of commanding power, a pioneer ready to break a lance for new music by publication and by performance. He conducted in western Europe, and his *Concerts Koussevitzky* in Paris were found a new and electrifying experience. When Dr. Koussevitzky assumed leadership of the Boston Symphony Orchestra in 1924, it was immediately evident that the future of the orchestra was in the hands of a leader of extraordinary courage and brilliance, a musician of sensitive sympathy and emotional penetration. The orchestra passed the half-century milestone with Koussevitzky at its head—more than one quarter of its years under his leadership. They have been years of a single and uninterrupted leadership, of stability in membership and of the coördination which these conditions have made possible. The present expansion of

the orchestra's activities is the result of these years. Extra-seasonal activities, including the foundation of a unique school, now leave only the month of September without concerts.

The orchestra's public and its influence in behalf of music have vastly grown. This has been accomplished without compromise. A great artist in the fullness of his day, Koussevitzky's art is always an adventure, a new testing.

It is the hope of the College that its members and friends at the Boston Session will take advantage of this unusual opportunity for an evening of fine music, and that their appreciation will be duly shown by an attendance filling Symphony Hall.

POST CONVENTION TOUR TO PLYMOUTH, THE PILGRIM SHORE, AND CAPE COD

(A continuation of the article from the February, 1941 issue of this journal)

For members and friends of the American College of Physicians, a post convention tour to Plymouth, the Pilgrim shore, and Cape Cod, has been arranged under the personal guidance of Mr. Leon V. Arnold, 36 Washington Square, West, New York City. The party will leave the Hotel Statler at 5:30 p.m., Friday, April 25, by de luxe motor coaches, visiting Plymouth, Sandwich, Barnstable, Yarmouth, Dennis, Brewster, Orleans, Provincetown, and other points of interest on Cape Cod, returning to Boston on Sunday, April 27.

The pulse always beats a little faster at the mention of Plymouth and the Pilgrim Shore. No places in America have greater historic and romantic appeal than Plymouth and her sister settlement, Jamestown. But because of the rigors of the climate, the hardships endured, and the results of the settlement there is probably the more sentiment about this early colony.

Cape Cod is quaint, precise. There is a dignity and primness in its villages. Its entire atmosphere takes you into the past by centuries and that is a long time before the Victorian era. The trip in Plymouth and along the North Shore of Cape Cod was described in the February issue of this Journal.

Provincetown.

After lunch we leave old Provincetown with its narrow winding streets, its picket fences and red chimneys, its gray gables and tiny gardens, its sand dunes and Town Hill surmounted by the granite shaft of Pilgrim Tower by the King's Highway. We return by the South Shore of the Cape which has a completely different aspect and character than the North. Less interesting? No, emphatically no.

At the very elbow of the Cape, sometimes called the funny bone, lies Chatham. You *must* pronounce both H's. Here William Nickerson of Yarmouth purchased a thousand acres of land from the Indian Sachem of the region by the down payment of a boat and in 1664 moved his family. Such a "concentration of wealth" placed him in difficulty with the General Court, but before he died he increased his holdings to

four thousand acres. Today Chatham is sophisticated but fascinating, a fashionable resort and very popular with the summer set. Here is the home of Joseph C. Lincoln whose books you have so much enjoyed.

As we swing west we get long glimpses of marine views. Many of the South Shore villages that we pass through were children of the earlier settlements of the North Shore to which today have been added the beautiful homes of the summer colonists.

Harwich was incorporated in 1694. It was the home of Captain Jonathan Walker, hero of Whittier's poem, "The Branded Hand." Today Harwich is the center of a great cranberry industry.

Along this shore sailed Gosnold in 1602 with his company of gentlemen adventurers. They made landings at various places with the intention of making a settlement, but there was dissension among them regarding a division of the spoils as well as trouble with the Indians and they loaded the ship with cedar, firs, and sassafras and returned to England. Later they returned to Jamestown.

Hyannis is the largest town of the Cape, its metropolis, and on all sides are estates and superbly located homes.

Pilgrim Hall, Plymouth.

Falmouth is another old town and a rich one, once the home of many deep-water sea captains whose stately homes still stand. Just across the sound lies Martha's Vineyard, one of New England's most loved resorts and as quaint a bit of land as one would expect to find a thousand miles distant.

From Falmouth we turn another corner and follow the shore of Buzzard's Bay, a beautifully broken coast line of little inlets and rocky, wooded capes. The first settlers were farmers and fishermen. The later settlers seek health and recreation. Among the most famous of these have been Joseph Jefferson and Grover Cleveland. Both lived on these shores and fished the Bay together.

At Bourne we cross the Canal and leave the Cape. Cape Cod begins at the Canal. Governor Bradford and Miles Standish knew this country well and in 1756 ninety Acadians who were exiles from their homes settled here.

Soon after leaving Plymouth on the morning of the 27th we stop in Duxbury to visit the Miles Standish Monument and the home of John Alden and Priscilla. En-route we see Marshfield, the home and tomb of Daniel Webster, the House of Old Oaken Bucket fame, the Old Ship Meeting House, 1681, said to be the oldest church in the United States. We follow the Ocean Shore Drive and Jerusalem Road and pass through Hingham, settled in 1635, and still retaining some of its colonial charm. In Quincy we visit the Adams Mansion, 1634, the home of John Adams and John Quincy Adams and reach Boston for the early afternoon train departures, completing our brief tour of "the Nation's Birthplace."

The price quoted, $27.75, includes absolutely every necessary expense. Even Webster would approve of the use of the term "absolutely," for you do not need to spend one nickel, not even for a tip, from Boston back to Boston.

If you have not already sent in your reservation, do it *NOW*. The accommodation remaining is limited. If you must change your plans later, your deposit will be refunded. This is a real opportunity that should not be passed up lightly.

Send your deposit or ask any questions that you may wish regarding the trip to Leon V. Arnold, 36 Washington Square West, New York City. Mr. Arnold will accompany the party.